CURA DEL CÁNCER AVANZADO CON INHIBIDORES DE PUNTOS DE CONTROL

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ESQUEMA

1. INTRODUCCIÓN
2. INHIBIDORES DEL PUNTO DE CONTROL
3. “SITUACIONES ESPECIALES”
4. ALGUNAS COMBINACIONES
5. CONCLUSIONES

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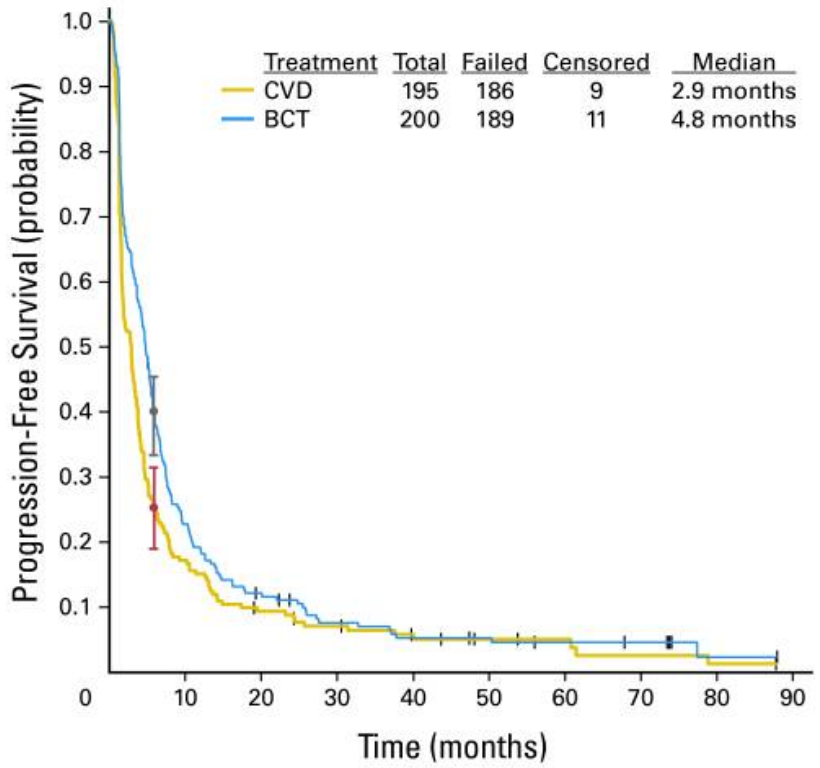
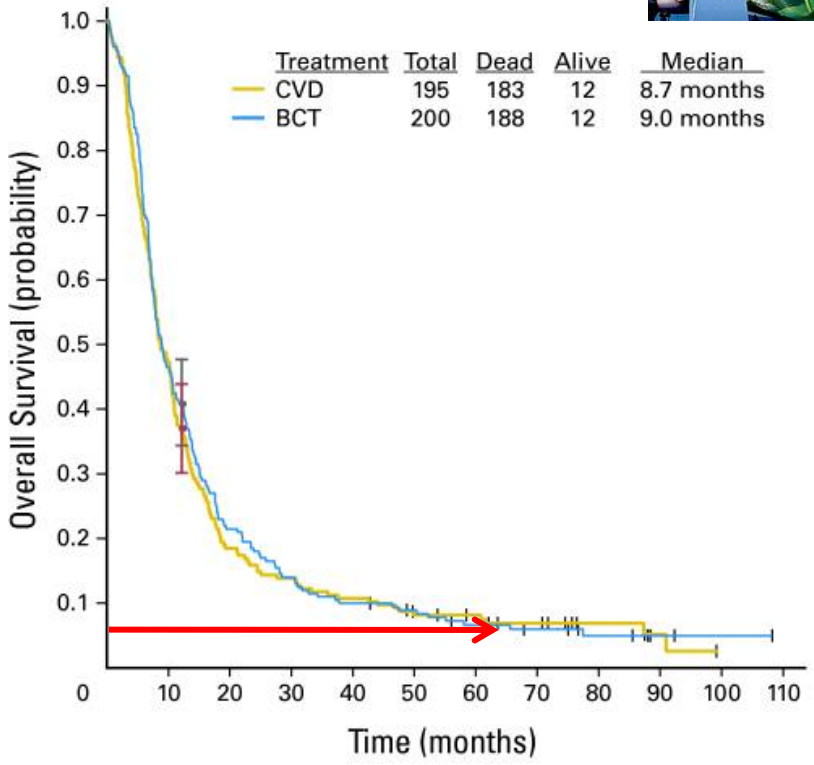
INTRODUCCIÓN

Melanoma avanzado y QT-IT





MB. Atkins et al. Phase III Trial Comparing Concurrent Biochemotherapy With Cisplatin, Vinblastine, Dacarbazine, Interleukin-2, and Interferon Alfa-2b With Cisplatin, Vinblastine, and Dacarbazine Alone in Patients With Metastatic Malignant Melanoma (E3695): A Trial Coordinated by the Eastern Cooperative Oncology Group. J. Clin. Oncol. 2008 Dec 10; 26(35): 5748–5754.

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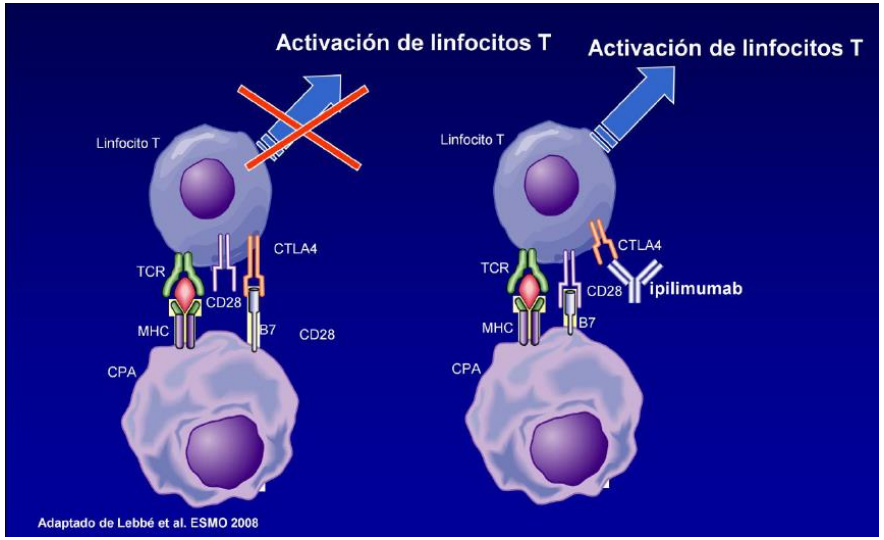
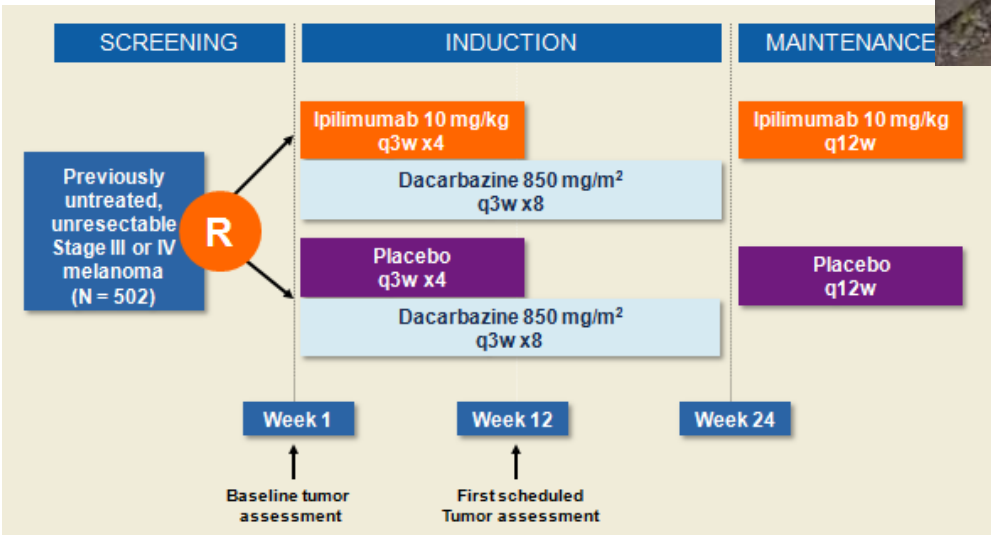
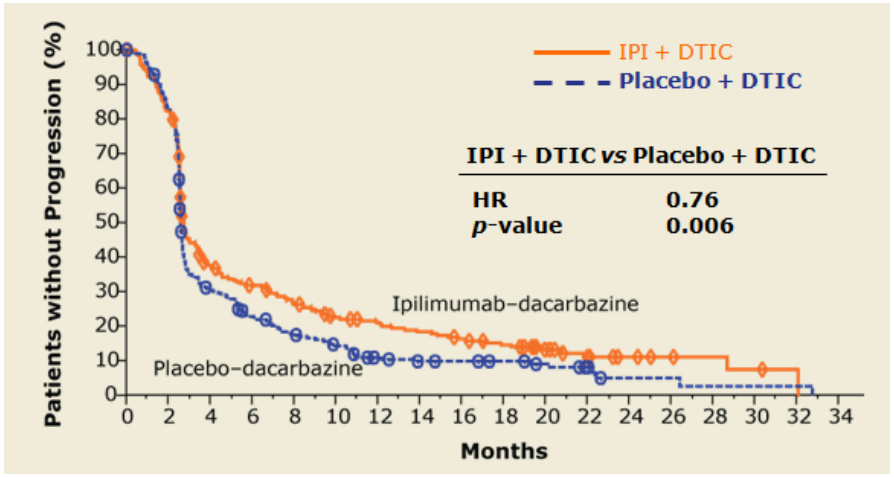
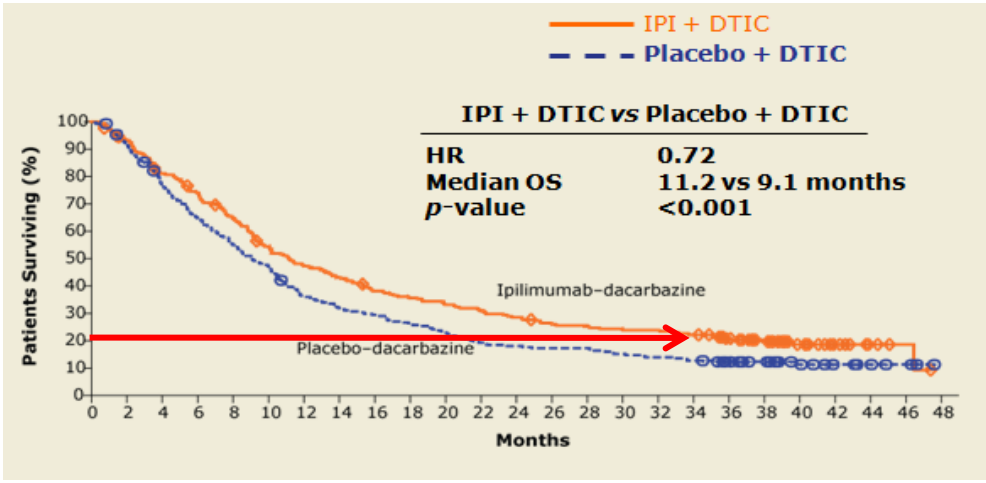
Anti-CTLA-4: Ipilimumab



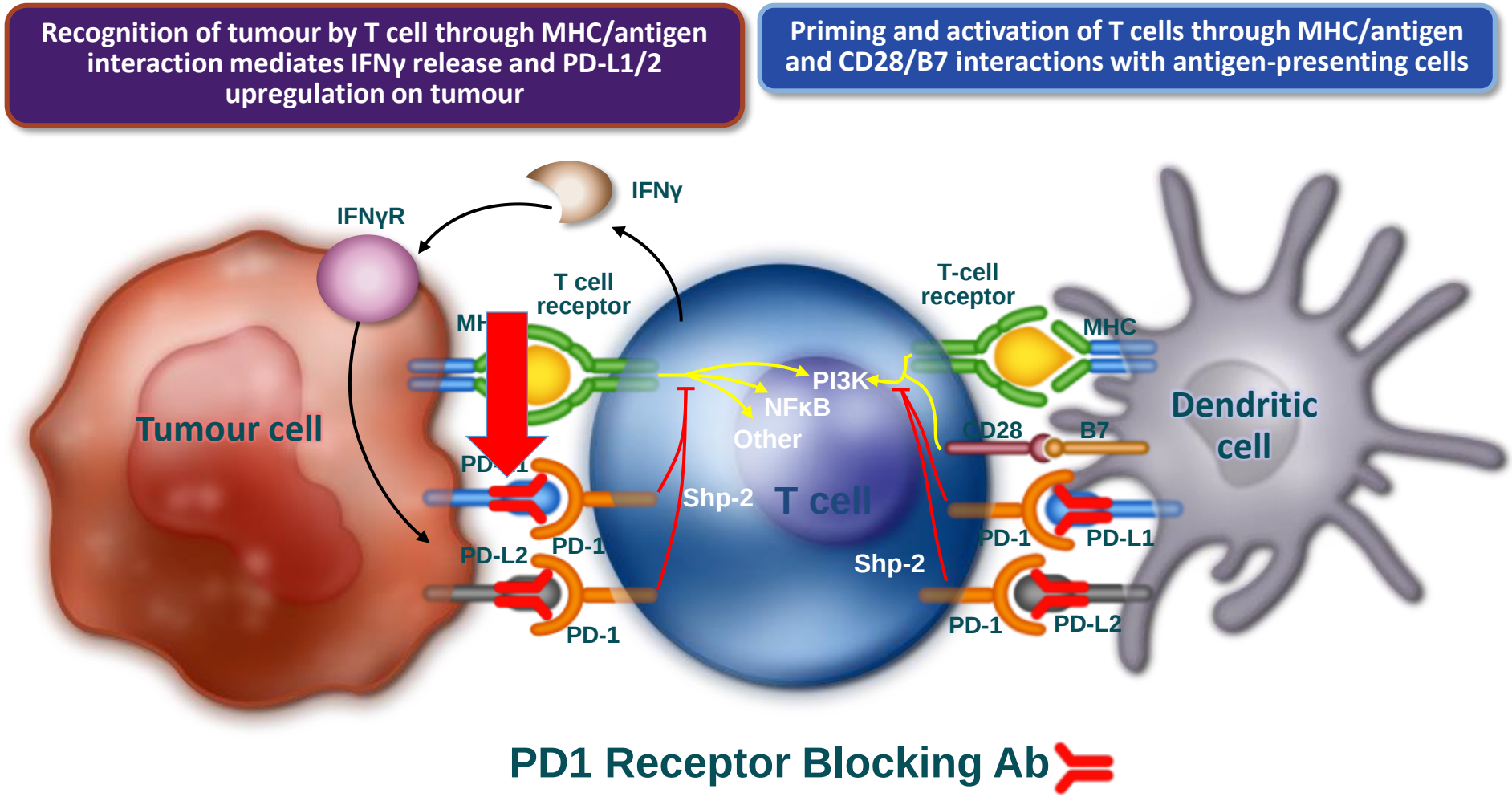




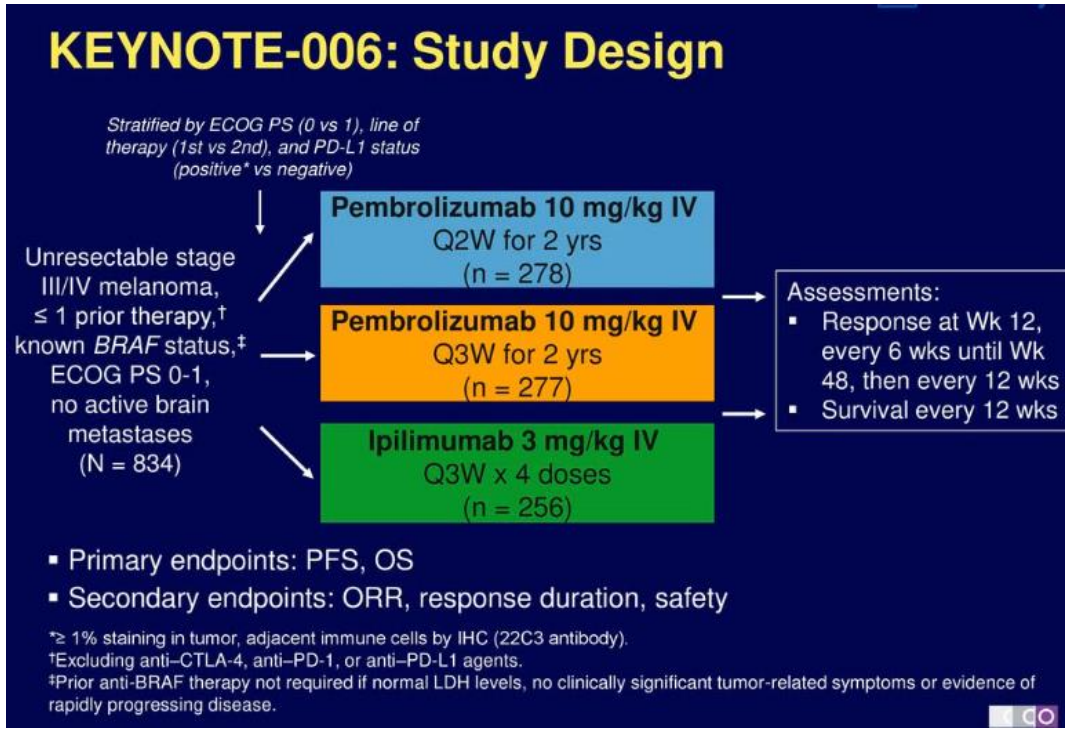


C. Robert et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med 2011; 364:2517-2526

Anti-PD-1/PD-L1



El melanoma avanzado y anti-PD-1



	Pembrolizumab n = 556	Ipilimumab n = 278
Age, median (range), y	62 (18-89)	62 (18-88)
Males, n (%)	335 (60)	162 (58)
ECOG PS 0, n (%)	384 (69)	188 (68)
Elevated LDH, n (%)	179 (32)	91 (33)
BRAF^{V600} mutant, n (%)	195 (35)	107 (38)
PD-L1 positive,[a] n (%)	446 (80)	225 (81)
M1c disease, n (%)	368 (66)	178 (64)
1 prior therapy,[b] n (%)	187 (34)[c]	97 (35)

GV Long et al.J. Clin Oncol 2018;36 (suppl;abstr 9503)

El melanoma avanzado y anti-PD-1

KEYNOTE-006

Figure 3. Modified PFS

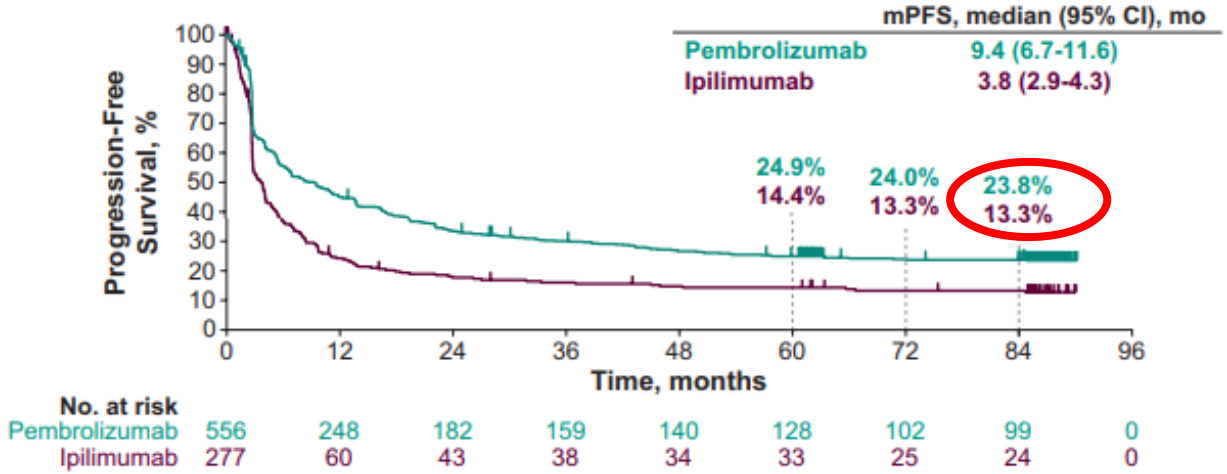
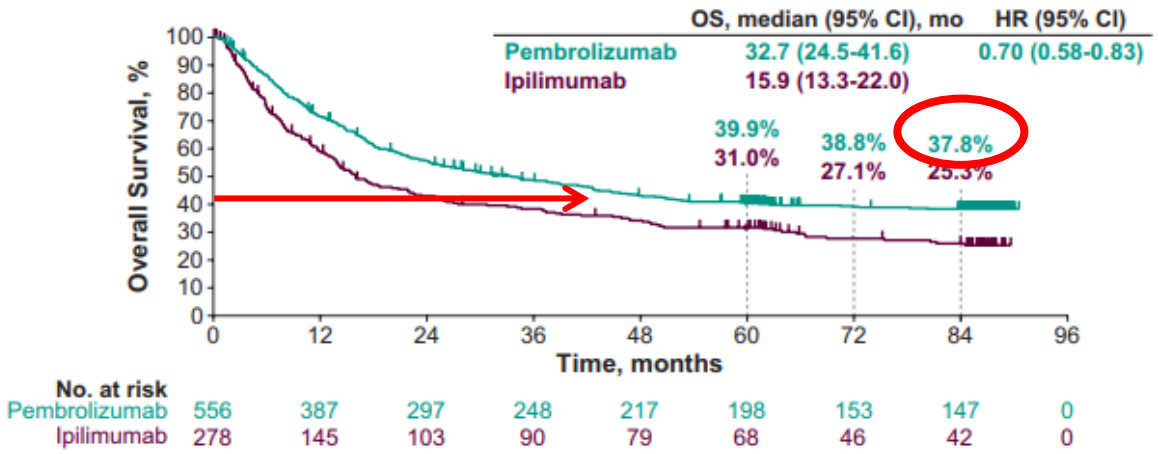


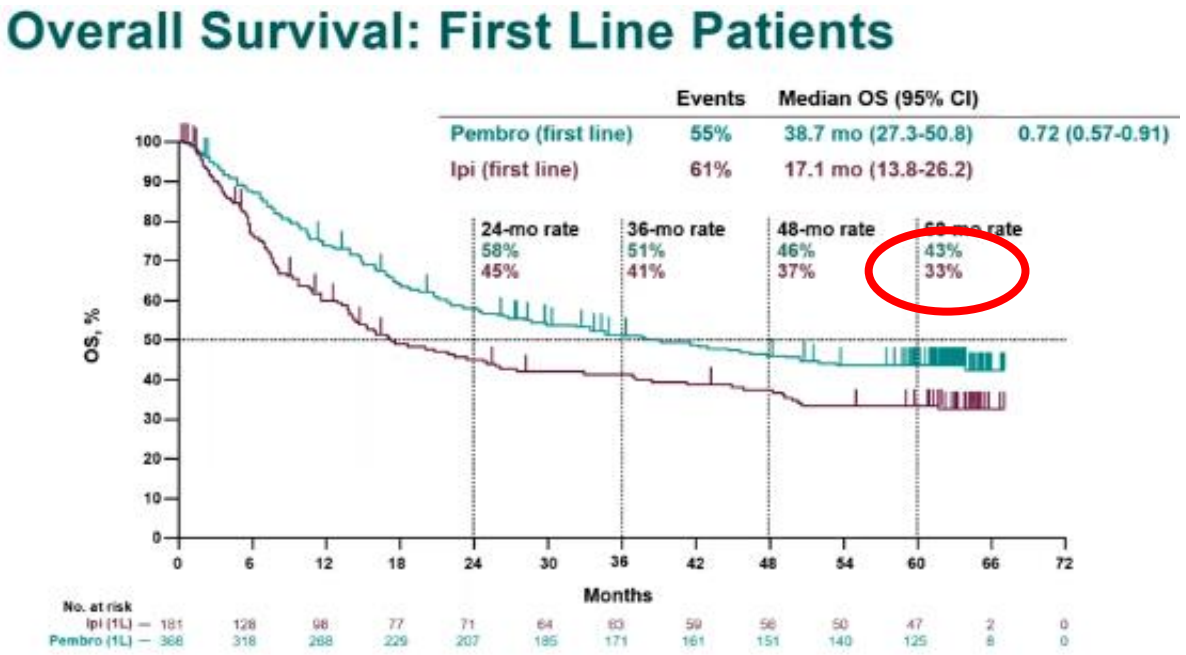
Figure 4. OS by Randomized Treatment in the Overall Population



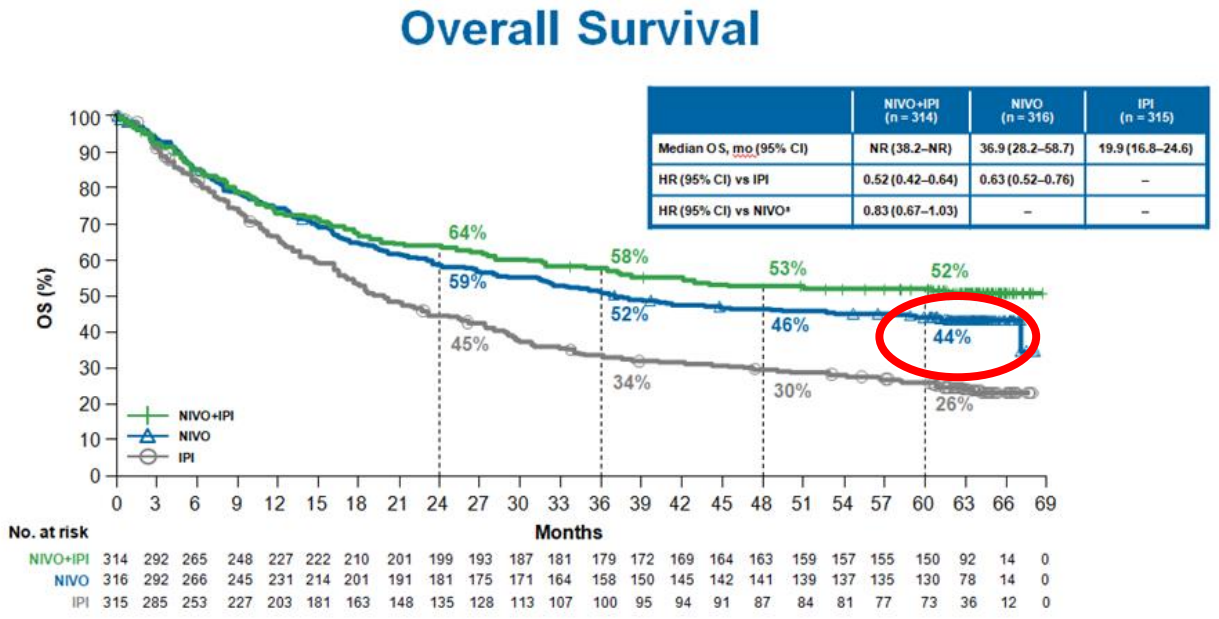
C. Robert et al. Presented at SMR 2021

Melanoma y antiPD-1

KEYNOTE-006



CHECKMATE-067



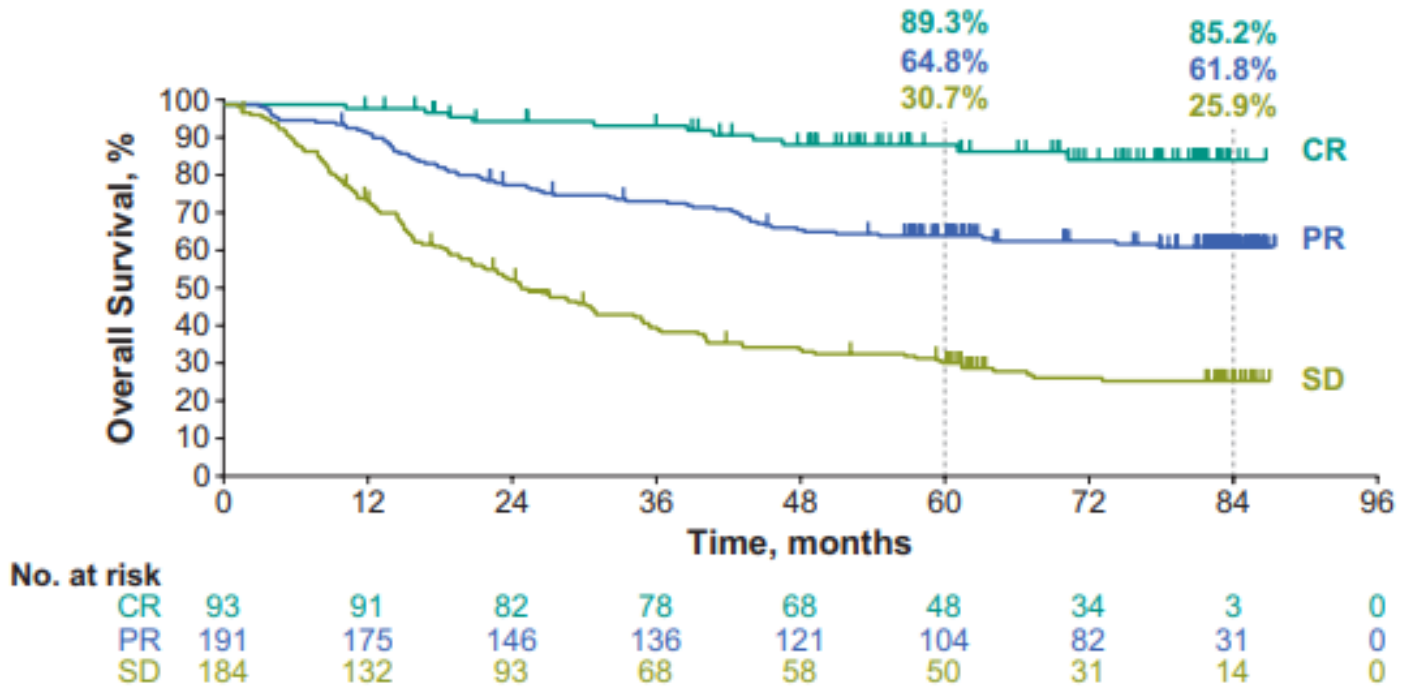
[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

GV Long et al Presented at ASCO 2020
J Larkin et al. Presented at ESMO 2019

El melanoma avanzado y anti-PD-1

KEYNOTE-006

Figure 5. OS From Best Overall Response by Best Overall Response in the Combined Pembrolizumab Population



C. Robert et al. Presented at SMR 2021

El melanoma avanzado y anti-PD-1

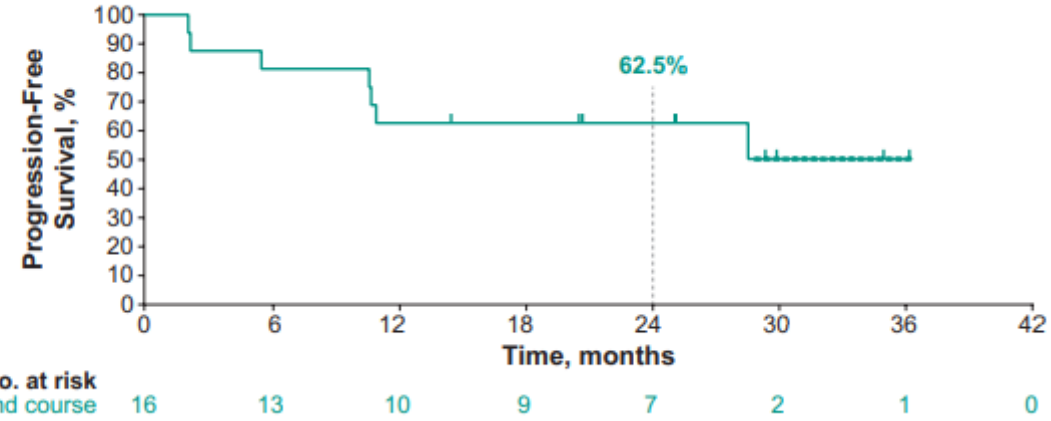
Table 3. Objective Response to Second-Course Treatment With Pembrolizumab per RECIST v1.1 by BICR

	Second Course n = 16
ORR, % (95% CI)	56.3 (29.9-80.2)
DCR, % (95% CI)[a]	87.5 (61.7-98.4)
Best overall response, n (%)	
CR	4 (25.0)
PR	5 (31.3)
SD	5 (31.3)
PD	2 (12.5)

BICR, blinded independent central review; ORR, objective response rate.
[a]Defined as CR + PR + SD.

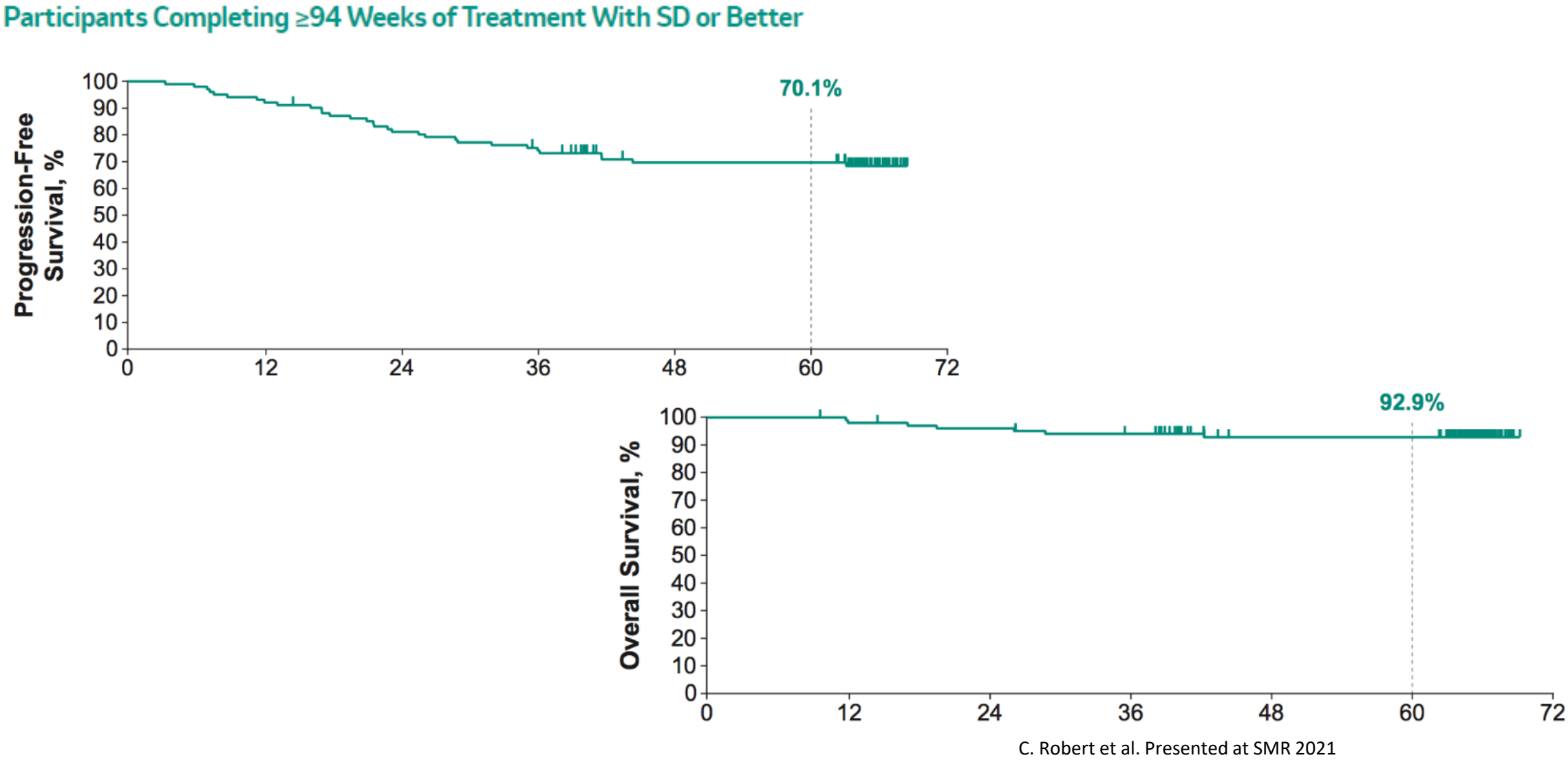
- Median time (range) to second-course treatment was 45.1 months (29.5-66.7)

Figure 8. PFS for Participants Receiving a Second Course of Pembrolizumab

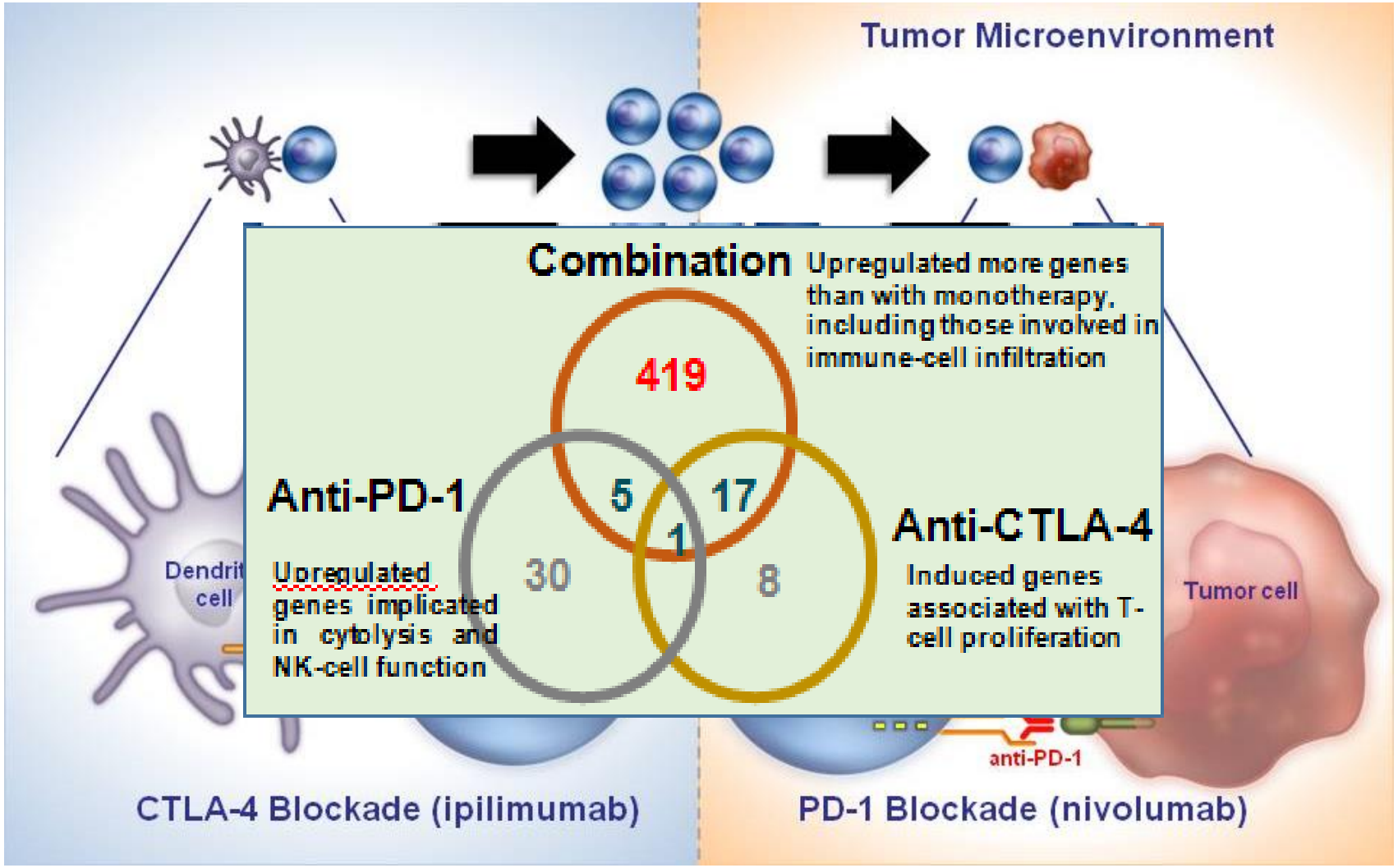


C. Robert et al. Presented at SMR 2021

El melanoma avanzado y anti-PD-1

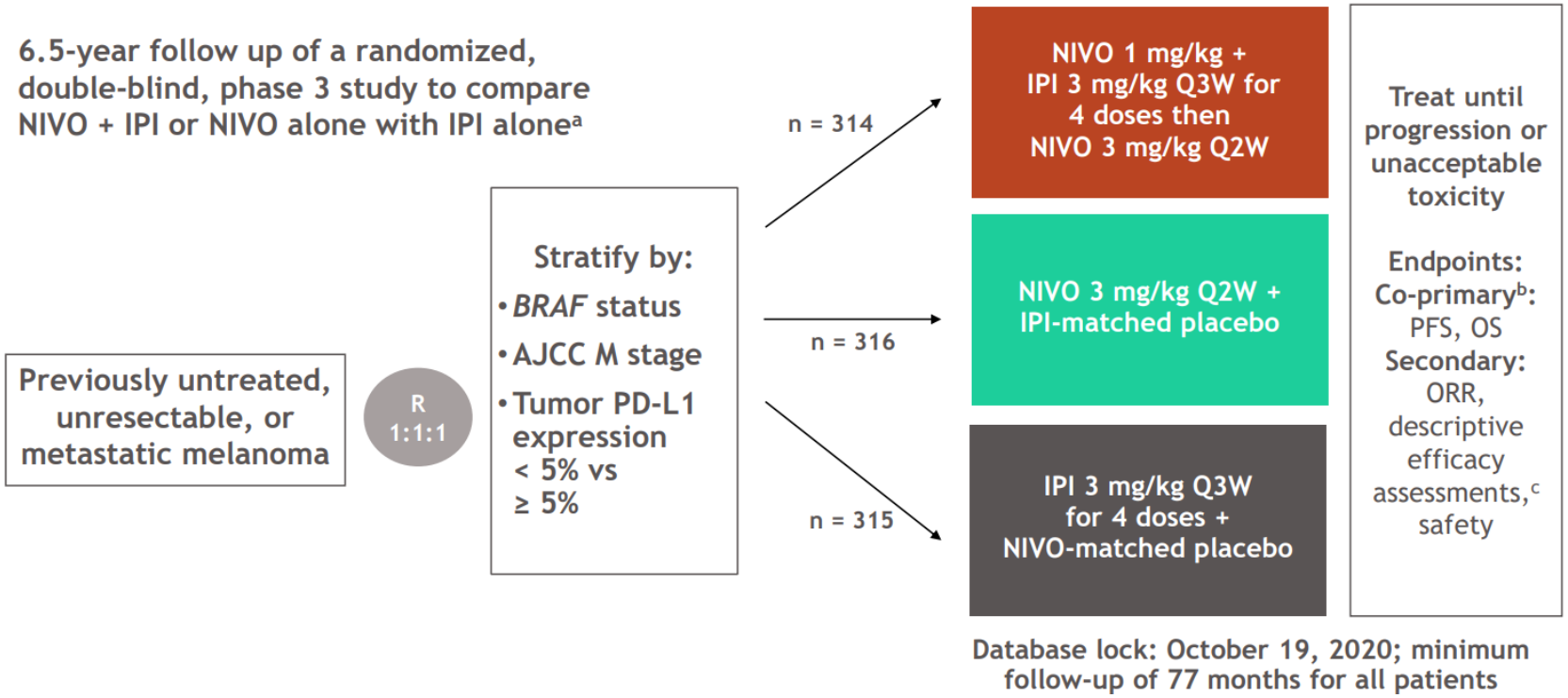


C. Robert et al. Presented at SMR 2021


Tumor Microenvironment
Combination
Upregulated more genes than with monotherapy, including those involved in immune-cell infiltration
419
Anti-PD-1
5
17
1
30
8
Anti-CTLA-4
Upregulated genes implicated in cytolysis and NK-cell function
Induced genes associated with T-cell proliferation
Dendrit cell
Tumor cell
anti-PD-1
CTLA-4 Blockade (ipilimumab)
PD-1 Blockade (nivolumab)

CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

CheckMate 067: study design

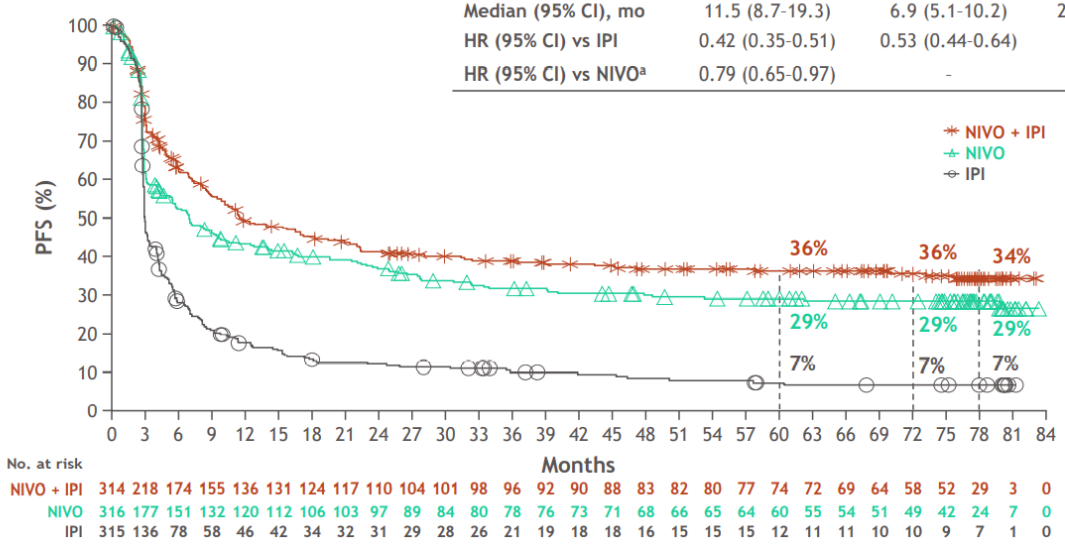


JD Wolchok et al. Presented at ASCO 2021

CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

Progression-free survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	11.5 (8.7-19.3)	6.9 (5.1-10.2)	2.9 (2.8-3.2)
HR (95% CI) vs IPI	0.42 (0.35-0.51)	0.53 (0.44-0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65-0.97)	-	-



Response to treatment at 6.5 years

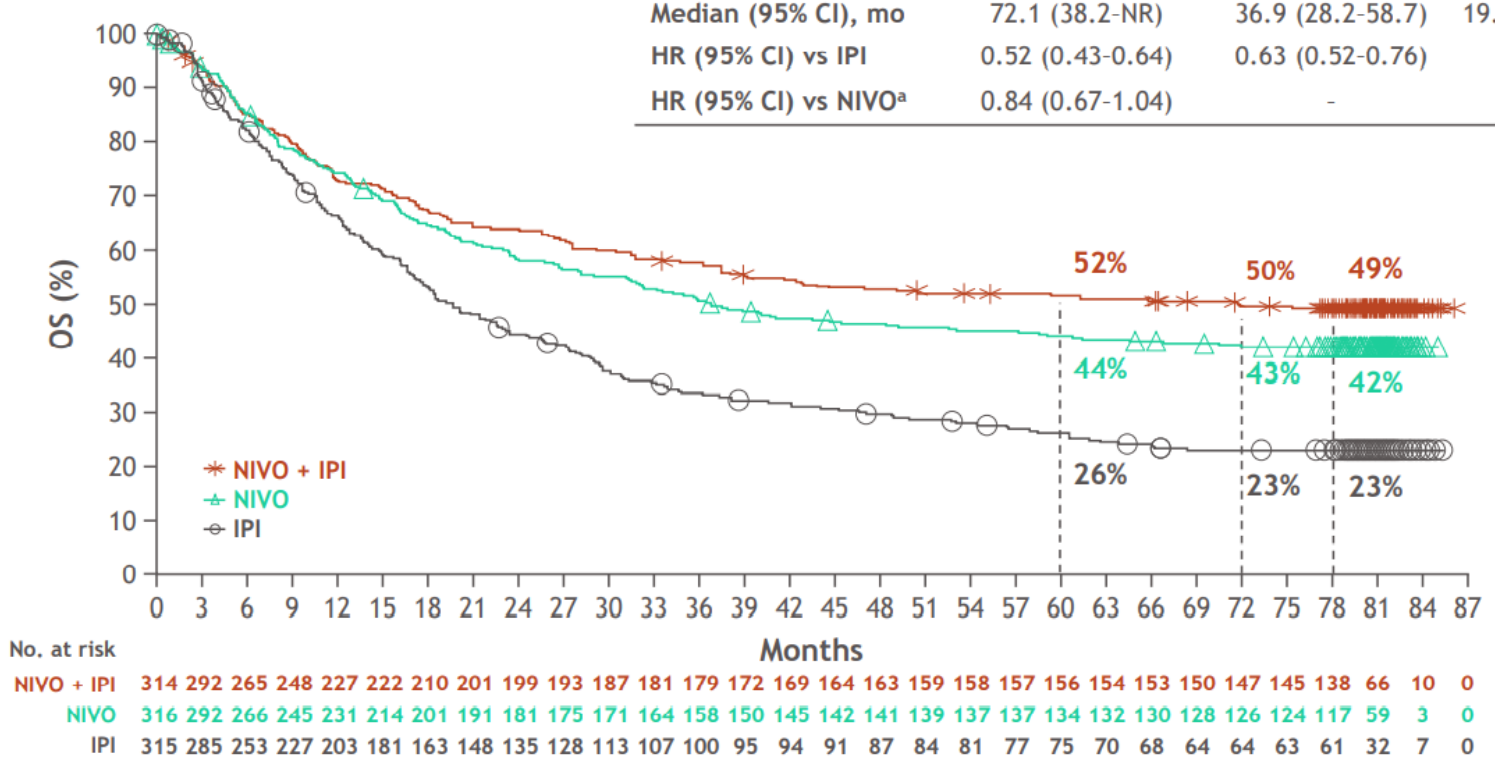
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53-64)	45 (39-51)	19 (15-24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
Median duration of response (95% CI), months	NR (61.9-NR)	NR (45.7-NR)	19.2 (8.8-47.4)

JD Wolchok et al. Presented at ASCO 2021

CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



JD Wolchok et al. Presented at ASCO 2021

CHECKMATE 067: 6.5-YEAR OUTCOMES IN PATIENTS WITH ADVANCED MELANOMA

Safety summary

- No new safety signals were observed
- No additional treatment-related deaths were reported since the 36-month analysis

	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO + IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1).
AE, adverse event.

JD Wolchok et al. Presented at ASCO 2021

CHECKMATE 067: TOXICIDAD

Table S5. Treatment-related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	Number of patients with event (%)					
Any treatment-related adverse event	300 (96)	186 (59)	271 (87)	73 (23)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	74 (24)	1 (<1)	69 (22)	5 (2)
Pruritus	112 (36)	6 (2)	72 (23)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	33 (11)	1 (<1)	16 (5)	0
Dry skin	15 (5)	0	17 (5)	0	11 (4)	0
Maculopapular rash	38 (12)	6 (2)	16 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	120 (38)	13 (4)	114 (36)	3 (1)	88 (28)	3 (1)
Asthenia	30 (10)	1 (<1)	26 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	30 (10)	70 (22)	9 (3)	106 (34)	18 (6)
Nausea	88 (28)	7 (2)	42 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	27 (9)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	41 (13)	26 (8)	8 (3)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	26 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	34 (11)	1 (<1)	22 (7)	0
Myalgia	18 (6)	1 (<1)	16 (5)	1 (<1)	9 (3)	0
Increased lipase	45 (14)	34 (11)	31 (10)	18 (6)	18 (6)	12 (4)
Increased amylase	26 (8)	9 (3)	22 (7)	7 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase	52 (17)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase	61 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	11 (4)	0	4 (1)	1 (<1)
Hypothyroidism	54 (17)	1 (<1)	32 (10)	0	14 (5)	0

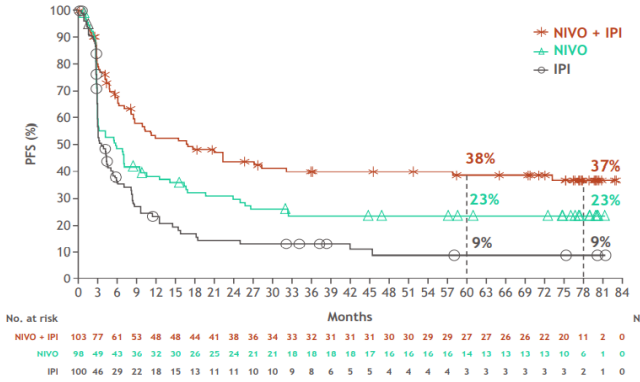
J. Larkin et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019, Appendix

CHECKMATE 067: 6.5-YEAR OUTCOMES IN PATIENTS WITH ADVANCED MELANOMA

PFS by *BRAF* mutation status[a]

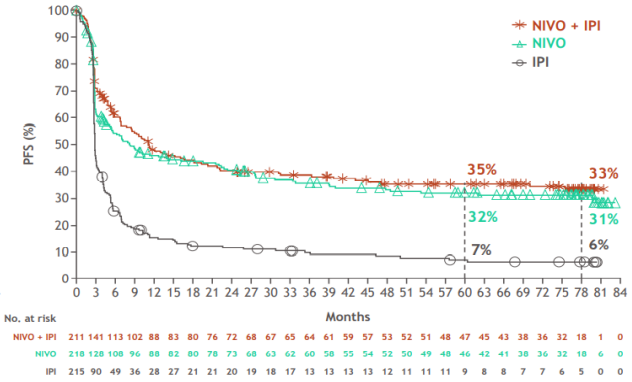
BRAF mutant

	NIVO + IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median (95% CI), mo	16.8 (8.3-32.0)	5.6 (2.8-9.5)	3.4 (2.8-5.2)
HR (95% CI) vs IPI	0.44 (0.31-0.62)	0.71 (0.51-0.98)	-
HR (95% CI) vs NIVO[b]	0.62 (0.44-0.89)	-	-



BRAF wild-type

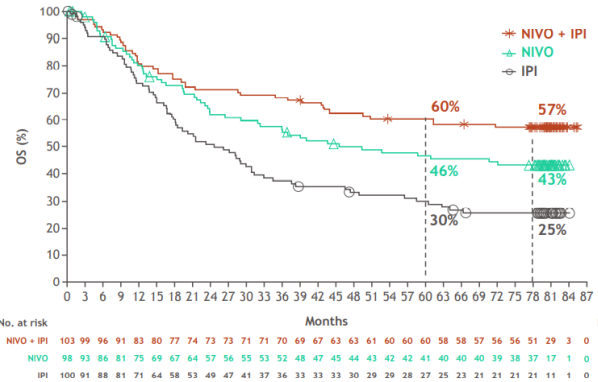
	NIVO + IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median (95% CI), mo	11.2 (7.0-18.1)	8.2 (5.1-19.6)	2.8 (2.8-3.1)
HR (95% CI) vs IPI	0.41 (0.33-0.52)	0.47 (0.38-0.59)	-
HR (95% CI) vs NIVO[b]	0.88 (0.69-1.12)	-	-



OS by *BRAF* mutation status[a]

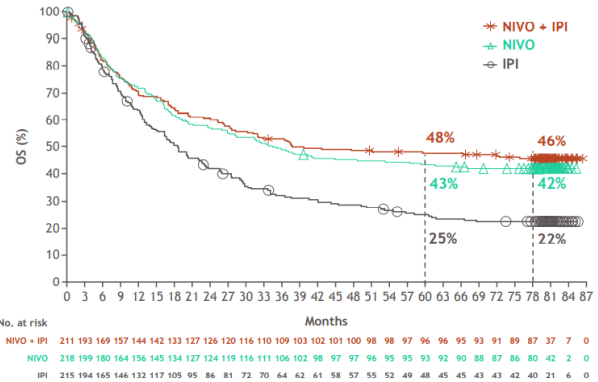
BRAF mutant

	NIVO + IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median (95% CI), mo	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI	0.43 (0.30-0.60)	0.63 (0.44-0.90)	-
HR (95% CI) vs NIVO[b]	0.68 (0.46-1.0)	-	-



BRAF wild-type

	NIVO + IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median (95% CI), mo	39.1 (27.5-NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI	0.58 (0.45-0.74)	0.63 (0.50-0.80)	-
HR (95% CI) vs NIVO[b]	0.92 (0.71-1.18)	-	-



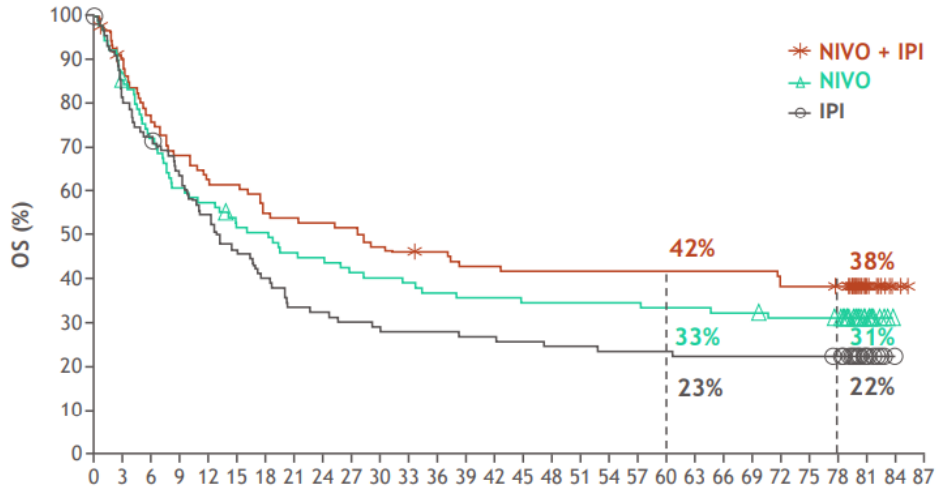
JD Wolchok et al. Presented at ASCO 2021

CHECKMATE 067: 6.5-YEAR OUTCOMES IN PATIENTS WITH ADVANCED MELANOMA

OS by presence of baseline liver metastases

With liver metastases

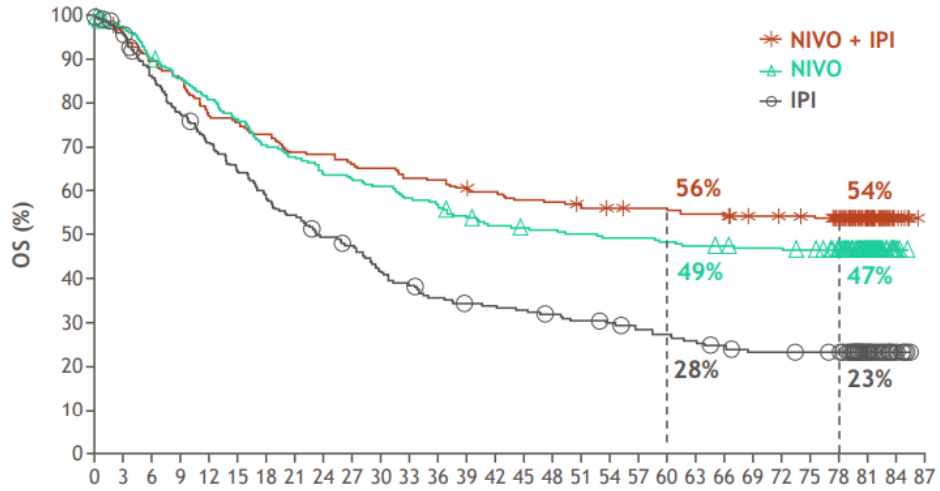
	NIVO + IPI (n = 93)	NIVO (n = 90)	IPI (n = 92)
Median (95% CI), mo	28.2 (15.2-71.9)	18.2 (8.1-32.3)	13.1 (9.6-18.4)
HR (95% CI) vs IPI	0.66 (0.46-0.93)	0.81 (0.58-1.14)	-
HR (95% CI) vs NIVO[a]	0.81 (0.56-1.16)	-	-



No. at risk																													
NIVO + IPI	93	81	69	62	57	56	50	49	48	47	43	42	41	38	38	37	37	37	37	37	37	37	37	35	34	33	11	2	0
NIVO	90	75	64	54	51	45	44	40	39	36	35	34	32	31	31	30	30	30	30	30	29	29	28	28	26	26	25	9	0	0
IPI	92	74	66	58	49	41	36	30	29	27	25	25	25	24	24	23	22	22	21	21	21	20	20	20	20	20	19	9	1	0

Without liver metastases

	NIVO + IPI (n = 221)	NIVO (n = 226)	IPI (n = 223)
Median (95% CI), mo	NR (50.7-NR)	52.7 (36.0-NR)	23.5 (18.6-29.4)
HR (95% CI) vs IPI	0.47 (0.37-0.60)	0.56 (0.44-0.71)	-
HR (95% CI) vs NIVO[a]	0.84 (0.64-1.09)	-	-



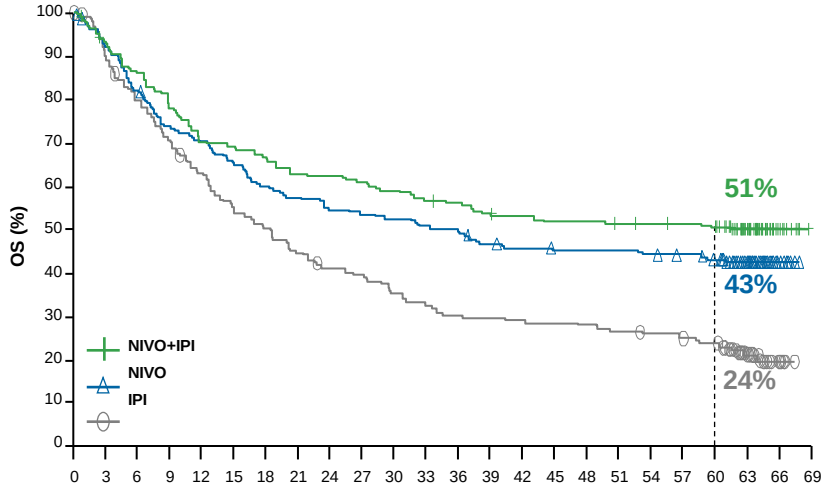
No. at risk																													
NIVO + IPI	221	211	196	186	170	166	160	152	151	146	144	139	138	134	131	127	126	122	121	120	119	117	116	113	112	111	105	55	8	0
NIVO	226	217	202	191	180	169	157	151	142	139	136	130	126	119	114	112	111	109	107	107	105	103	102	100	100	98	92	50	3	0
IPI	223	211	187	169	154	140	127	118	106	101	88	82	75	71	70	68	65	62	60	56	54	50	48	44	44	43	42	23	6	0

JD Wolchok et al. Presented at ASCO 2021

CHECKMATE 067: OS BY TUMOR PD-L1 EXPRESSION, 5% CUTOFF

PD-L1 < 5%

	NIVO+IPI (n = 210)	NIVO (n = 208)	IPI (n = 202)
Median, mo (95% CI)	NR (32.7–NR)	35.9 (23.1–59.2)	18.4 (13.7–22.5)
HR (95% CI) vs IPI	0.50 (0.39–0.65)	0.62 (0.49–0.79)	–
HR (95% CI) vs NIVO[a]	0.81 (0.62–1.06)	–	–

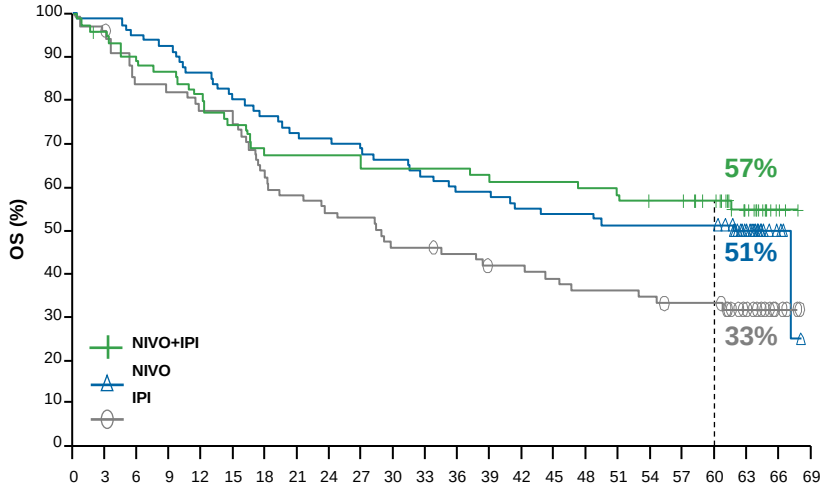


No at risk

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	116	111	109	106	106	104	103	102	101	61	9	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	102	95	92	90	90	90	88	86	82	48	9	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	59	58	57	56	55	52	50	48	45	19	5	0

PD-L1 ≥ 5%

	NIVO+IPI (n = 68)	NIVO (n = 80)	IPI (n = 75)
Median, mo (95% CI)	NR (39.1–NR)	61.6 (33.6–NR)	28.9 (18.1–44.2)
HR (95% CI) vs IPI	0.58 (0.37–0.91)	0.63 (0.42–0.96)	–
HR (95% CI) vs NIVO[a]	0.91 (0.57–1.46)	–	–



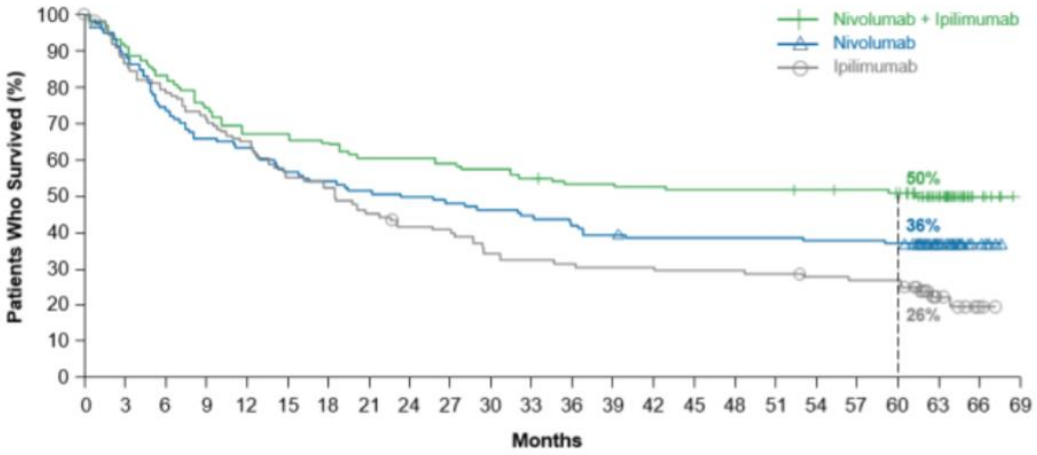
No. at risk

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	42	41	41	40	38	37	36	33	20	2	0
NIVO	80	79	76	74	69	64	61	58	57	54	53	50	47	46	44	43	43	41	41	41	41	26	5	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	32	29	29	27	25	25	24	22	22	12	5	0

J. Larkin et al. Presented at ESMO 2019

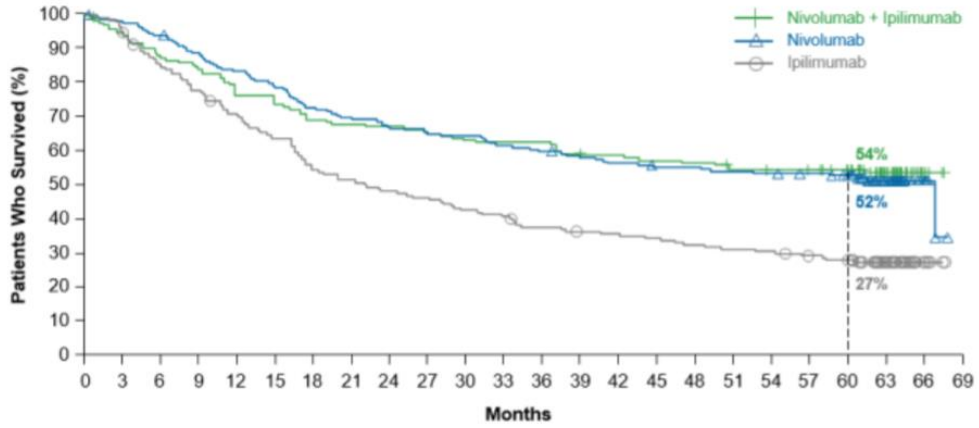
Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

(A) PD-L1 expression level <1%



No. at risk																							
Nivolumab + Ipilimumab	123	113	102	91	82	82	79	74	74	72	70	67	65	64	63	62	62	62	61	60	59	35	6	0
Nivolumab	117	103	86	76	73	65	62	59	57	55	53	51	49	45	43	43	43	43	42	42	41	24	5	0
Ipilimumab	113	96	87	79	71	61	57	50	44	43	36	34	33	32	32	31	31	30	28	27	27	9	3	0

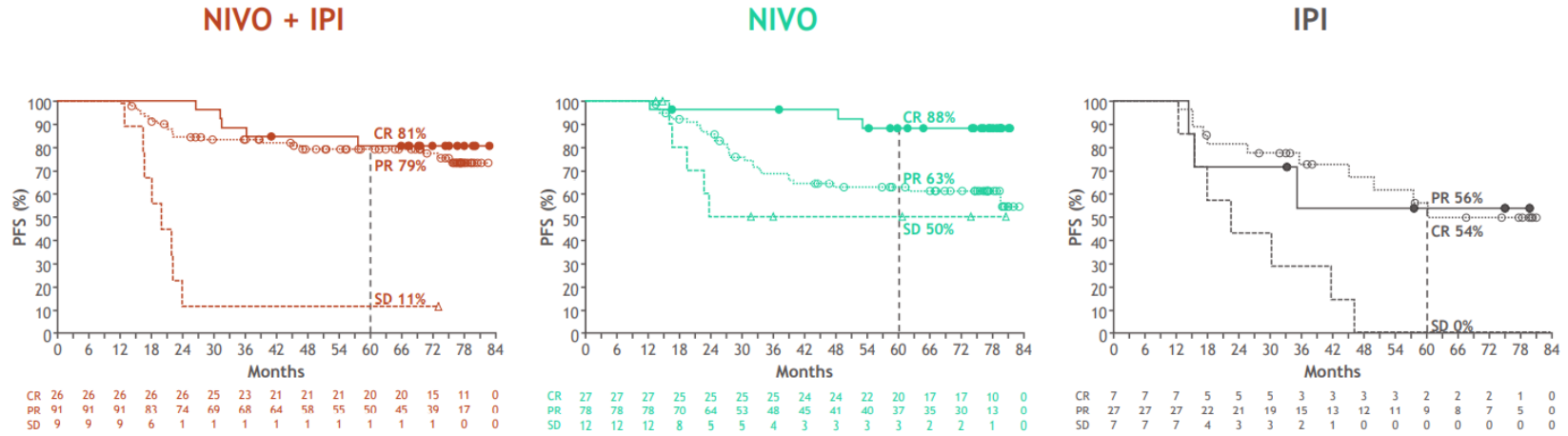
(B) PD-L1 expression level ≥1%



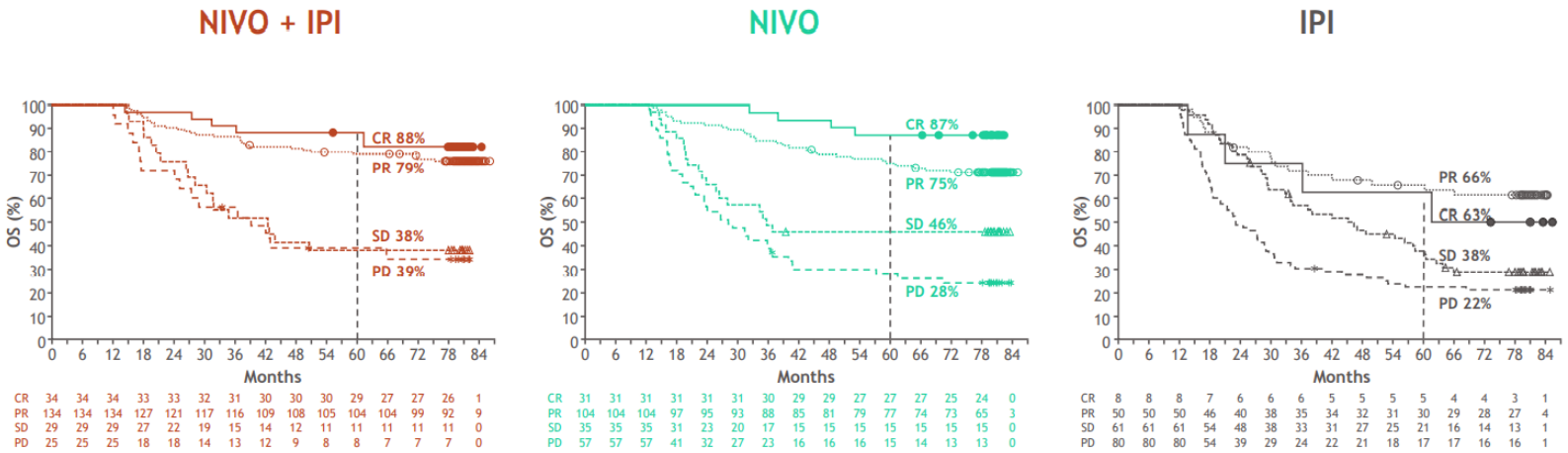
No. at risk																							
Nivolumab + Ipilimumab	155	144	132	127	116	112	105	102	101	99	96	94	94	89	87	85	84	80	79	78	75	46	5	0
Nivolumab	171	165	159	149	140	132	122	117	112	109	108	103	100	96	93	90	90	88	87	85	82	50	9	0
Ipilimumab	164	155	137	125	113	101	88	82	76	73	67	64	58	55	54	52	49	47	46	43	40	22	7	0

J Larkin et al. New Engl J Med, 2019

CHECKMATE 067: 6.5-YEAR OUTCOMES IN PATIENTS WITH ADVANCED MELANOMA



- Patients with a best overall response of a CR, PR, or SD at 12 months were followed for PFS[b]

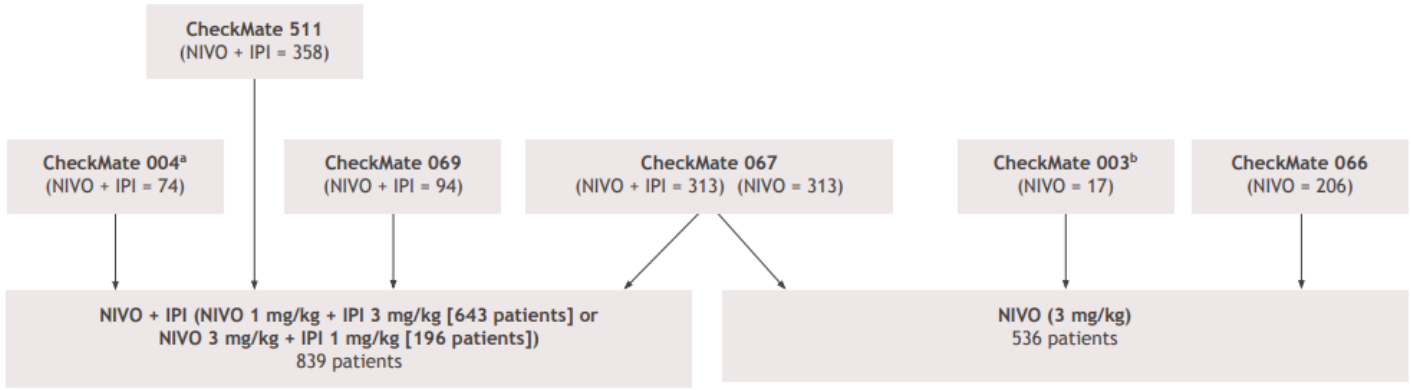


- Patients with a best overall response of a CR, PR, SD, or PD at 12 months were followed for OS

JD Wolchok et al. Presented at ASCO 2021

Pooled long-term outcomes with nivolumab plus ipilimumab (NIVO + IPI) and NIVO in advanced melanoma

Study overview



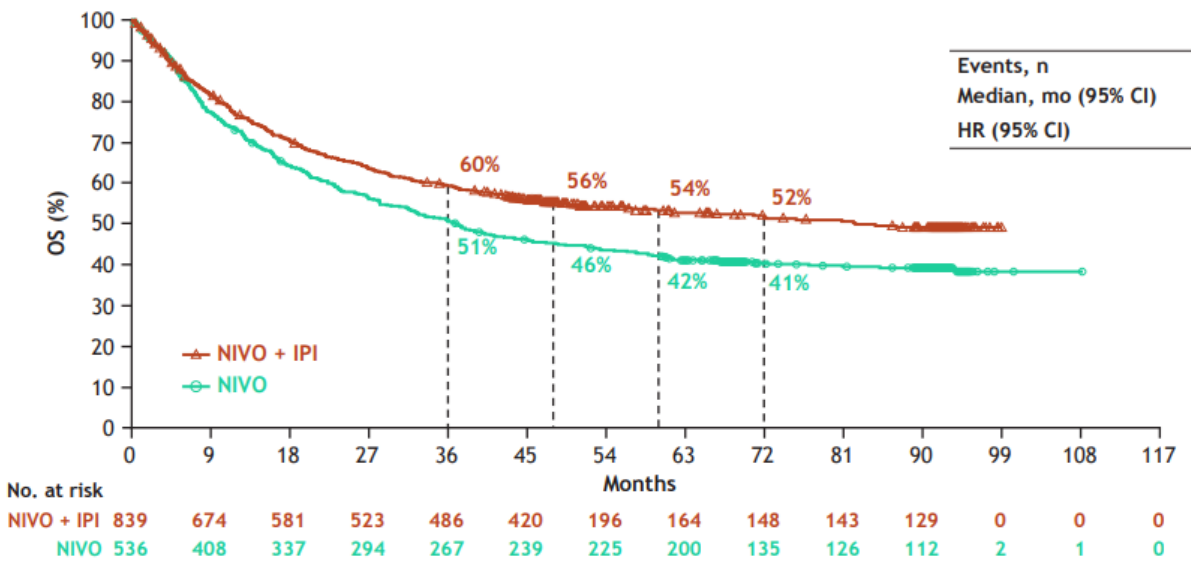
- ICI-treatment-naive patients with advanced melanoma with or without stable brain metastases received NIVO + IPI or NIVO monotherapy
- An OS Kaplan-Meier curve on the pooled data was generated
- An analysis of clinically relevant baseline characteristics for OS was conducted using univariate and multivariate models for each treatment group separately
- A classification and regression tree analysis was used to separate patients into different risk groups to determine potential predictors for survival

Although all patients included in this pooled analysis were ICI-treatment-naive, patients may have received other prior non-ICI systemic therapy. CheckMate 067, 069, 511, and 066 enrolled patients previously untreated for advanced melanoma. [a]Sixteen patients who received NIVO 3 mg/kg from cohort 7 were excluded because they were not ICI-treatment-naive. [b]Only patients who received NIVO 3 mg/kg were included.

Long et al SMR 2022

Pooled long-term outcomes with nivolumab plus ipilimumab (NIVO + IPI) and NIVO in advanced melanoma

OS in all treated patients



	NIVO + IPI (n = 839)	NIVO (n = 536)
Events, n	386	315
Median, mo (95% CI)	84.6 (59.5-NR)	36.9 (31.2-45.7)
HR (95% CI)	0.78 (0.67-0.91)	

- Median follow-up for OS was 45.0 months (range, 0.1-99.0) for NIVO + IPI and 35.8 months (range, 0.3-108.2) for NIVO monotherapy
  - 369/839 (44%) patients who received NIVO + IPI and 168/536 (31%) who received NIVO monotherapy remained in follow-up
- OS for the pooled population was longer with NIVO + IPI vs NIVO monotherapy (median 84.6 months vs 36.9 months, respectively)

Heavy censoring occurred at various time points because of the different length of follow-up for each study.

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Pooled long-term outcomes with nivolumab plus ipilimumab (NIVO + IPI) and NIVO in advanced melanoma

OS multivariate analysis

		NIVO + IPI		NIVO	
Baseline factor	**Subgroup**	**HR (95% CI)[a]**	***P* value[b]**	**HR (95% CI)[a]**	***P* value[b]**
Sex	Male vs. female	NA	NA	0.80 (0.62-1.02)	0.0765
Age, years	≥ 65 vs < 65	1.38 (1.11-1.70)	0.0035	NA	NA
BRAF status	Wild-type vs mutant	1.22 (0.98-1.54)	0.0815	NA	NA
M stage	M0/M1A/M1B vs M1C	0.80 (0.63-1.02)	0.0693	0.76 (0.55-1.03)	0.0789
PD-L1 status	≥ 5% vs < 5%	NA	NA	0.63 (0.47-0.83)	0.013
ECOG PS	ECOG PS ≥ 1 vs ECOG PS = 0	1.59 (1.27-2.00)	< 0.0001	1.91 (1.45-2.52)	< 0.0001
Baseline LDH	LDH > ULN vs LDH ≤ ULN	1.81 (1.45-2.25)	< 0.0001	1.63 (1.24-2.15)	0.0004
Liver metastases	Yes vs no	1.18 (0.93-1.50)	0.1749	1.55 (1.15-2.09)	0.0037
Region[c]	Europe vs North America	1.57 (1.16-2.13)	0.0037	0.97 (0.70-1.35)	0.8525
	Other vs Europe	0.43 (0.28-0.67)	0.0002	0.56 (0.39-0.81)	0.0019
	Other vs North America	0.68 (0.41-1.12)	0.1324	0.55 (0.35-0.84)	0.0066

- Factors associated with longer OS:
  - NIVO + IPI: Age < 65 years, ECOG PS score 0, baseline LDH ≤ ULN, and region (North America [vs Europe] and Other [vs Europe])
  - NIVO: PD-L1 ≥ 5%, ECOG PS 0, baseline LDH ≤ ULN, no liver metastases, and region (Other [vs Europe] and Other [vs North America])

NA (not applicable) findings (from the UVA) were not statistically significant, and therefore were not entered into the MVA.
[a]HRs and 95% CIs were calculated using the Full Cox Proportional Hazards Multivariate Regression method, based on significant baseline factors ($P \leq 0.10$) from the UVA. [b]P value < 0.05, statistical significance at 0.05 nominal level. [c]Other regions included Argentina, Australia, Chile, Israel, and New Zealand.

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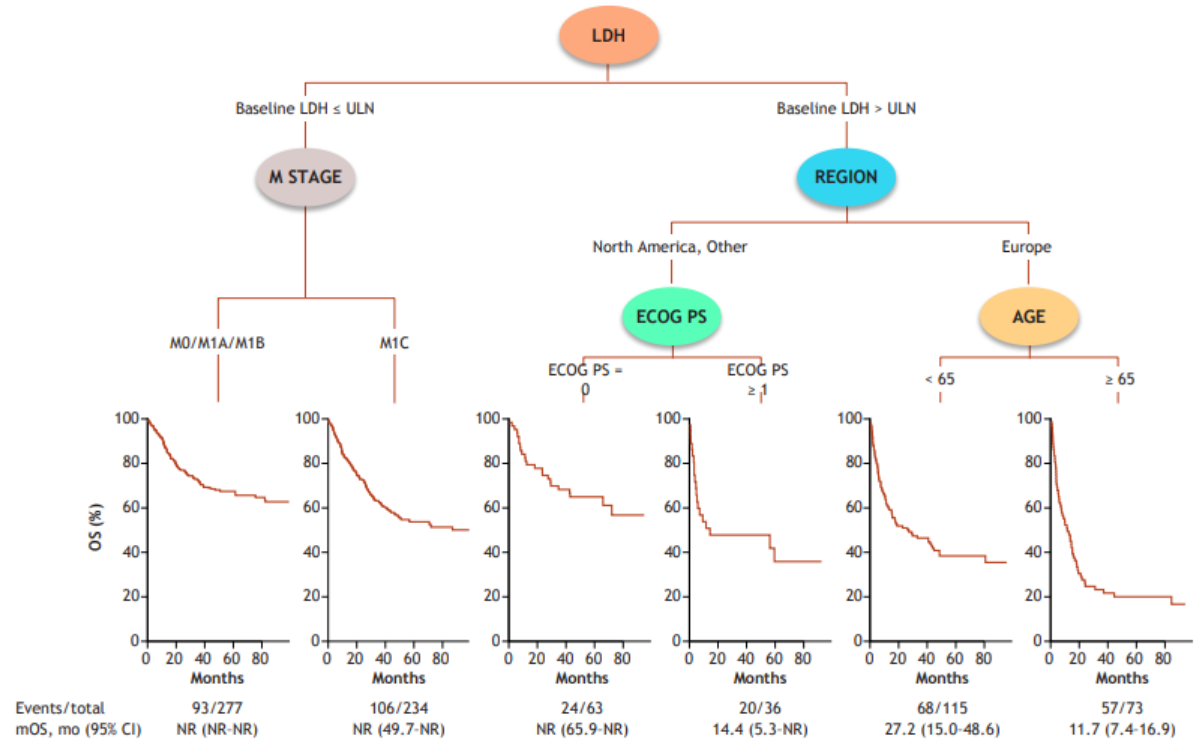
Pooled long-term outcomes with nivolumab plus ipilimumab (NIVO + IPI) and NIVO in advanced melanoma

OS classification and regression tree analysis in patients treated with NIVO + IPI



- In patients treated with NIVO + IPI, the most favorable subgroup identified in the CART analysis was patients with LDH ≤ ULN and stage M0/M1A/M1B disease

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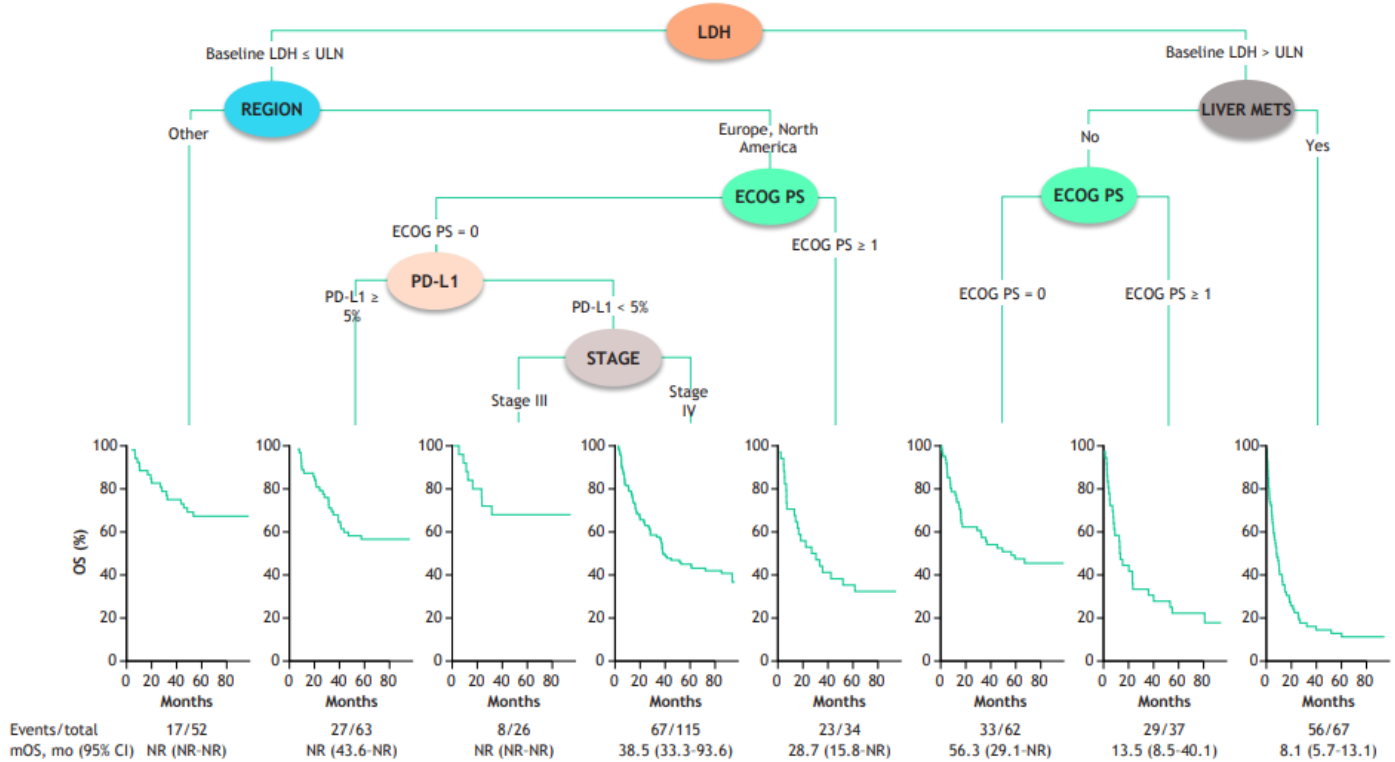
Pooled long-term outcomes with nivolumab plus ipilimumab (NIVO + IPI) and NIVO in advanced melanoma

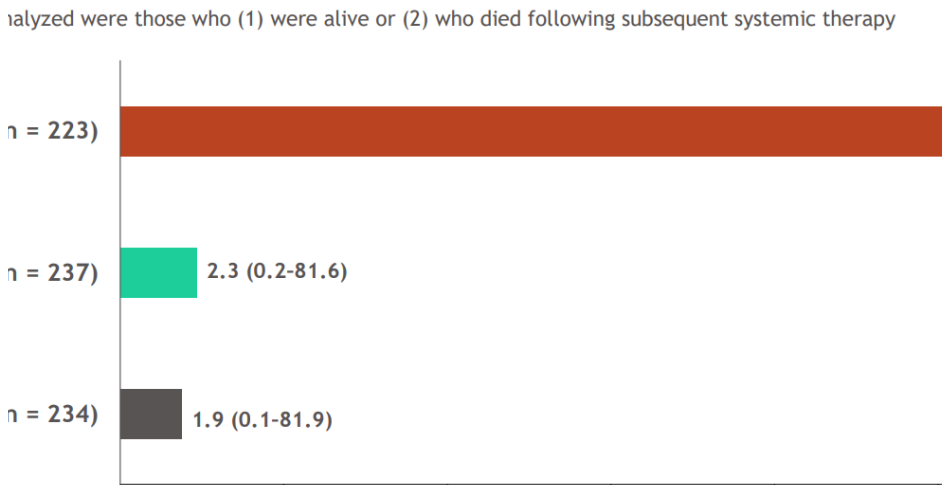
OS classification and regression tree analysis in patients treated with NIVO



- In patients treated with NIVO, the most favorable subgroup identified was patients with baseline LDH ≤ ULN and in 'Other' regions

Long et al SMR 2022

CHECKMATE 067: 6.5-YEAR OUTCOMES IN PATIENTS WITH ADVANCED MELANOMA

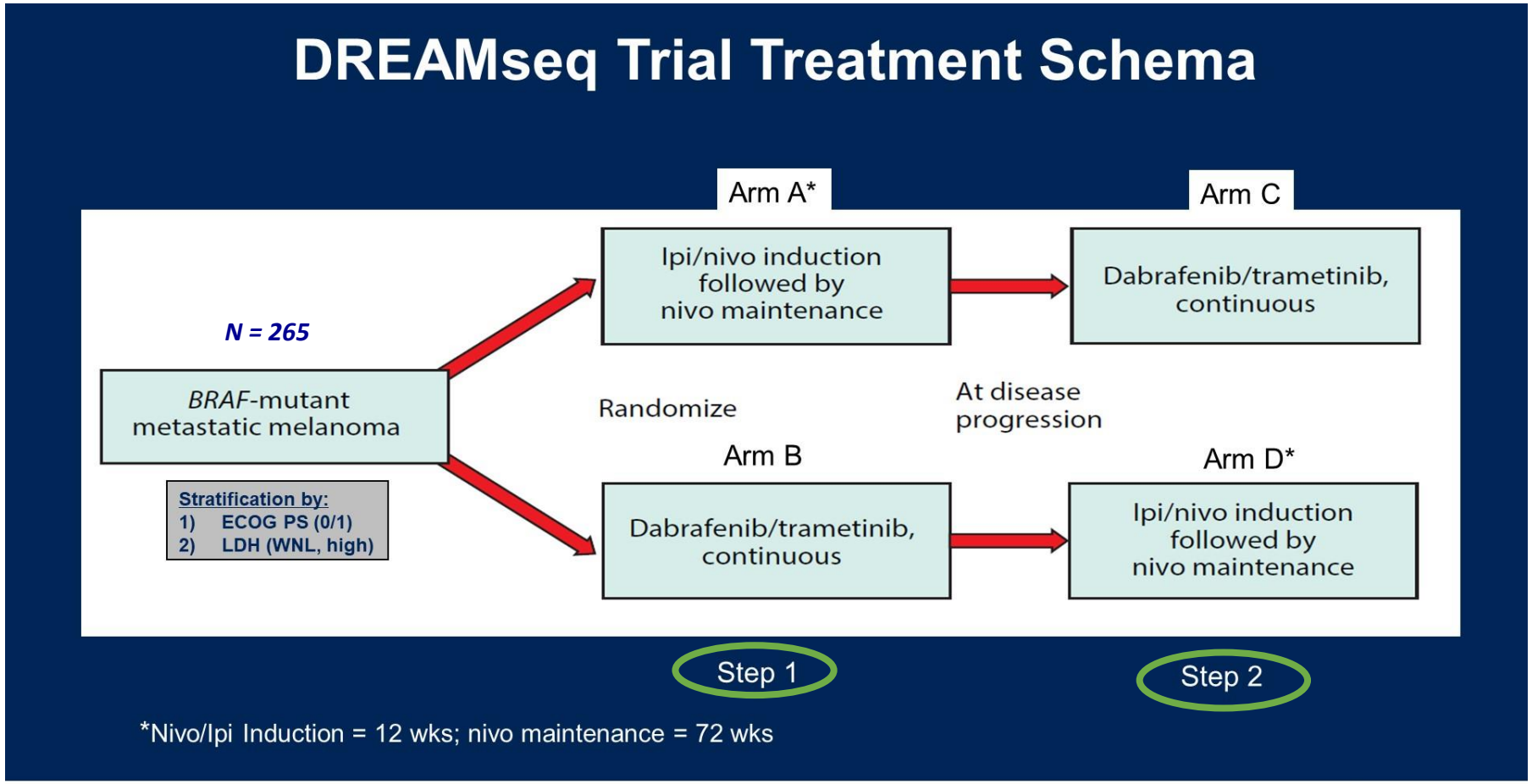


JD Wolchok et al. Presented at ASCO 2021

ESQUEMA

1. INTRODUCCIÓN
2. INHIBIDORES DEL PUNTO DE CONTROL
3. **“SITUACIONES ESPECIALES”**
4. ALGUNAS COMBINACIONES
5. CONCLUSIONES

DREAMseq: *Nivo/Ipi vs Dabra/Trame in 1st line*



Objetivo 1º:
- 2-year OS

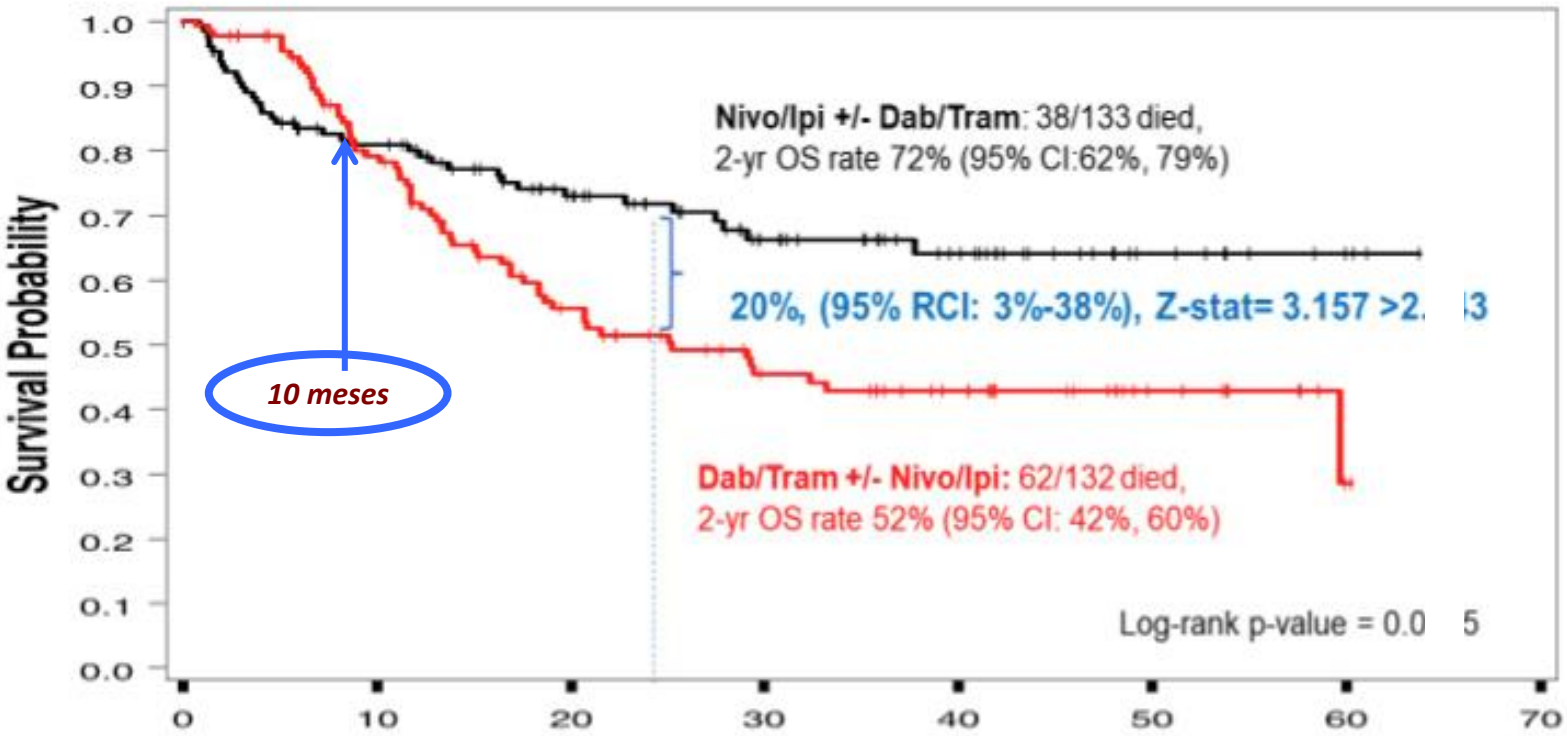
Objetivos 2º:
- 3-year OS.
- ORR y PFS
- Activity 2nd lines.

Atkins M. J Clin Oncol 39, 2021 (suppl 36; abstr 356154*)*

DREAMseq: *Nivo/Ipi vs Dabra/Trame in 1st line*

Overall Survival (OS): Step 1 +/- Step 2

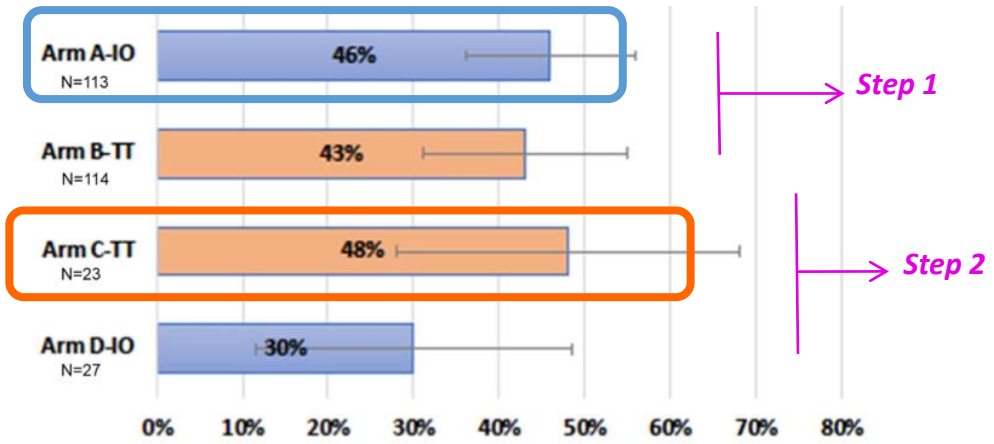
	Nivo/Ipi	Dab/Tram
2-year OS rate	72%	52%
p-value	0,0095	



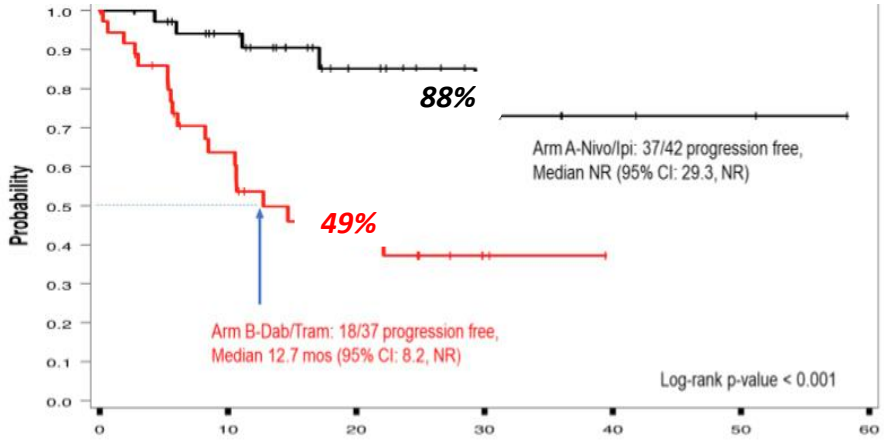
Atkins M. J Clin Oncol 39, 2021 (suppl 36; abstr 356154)

DREAMseq: *Nivo/Ipi vs Dabra/Trame in 1st line*

ORR (%) By Treatment Arm*



Duration of Response (DOR)*: Step1



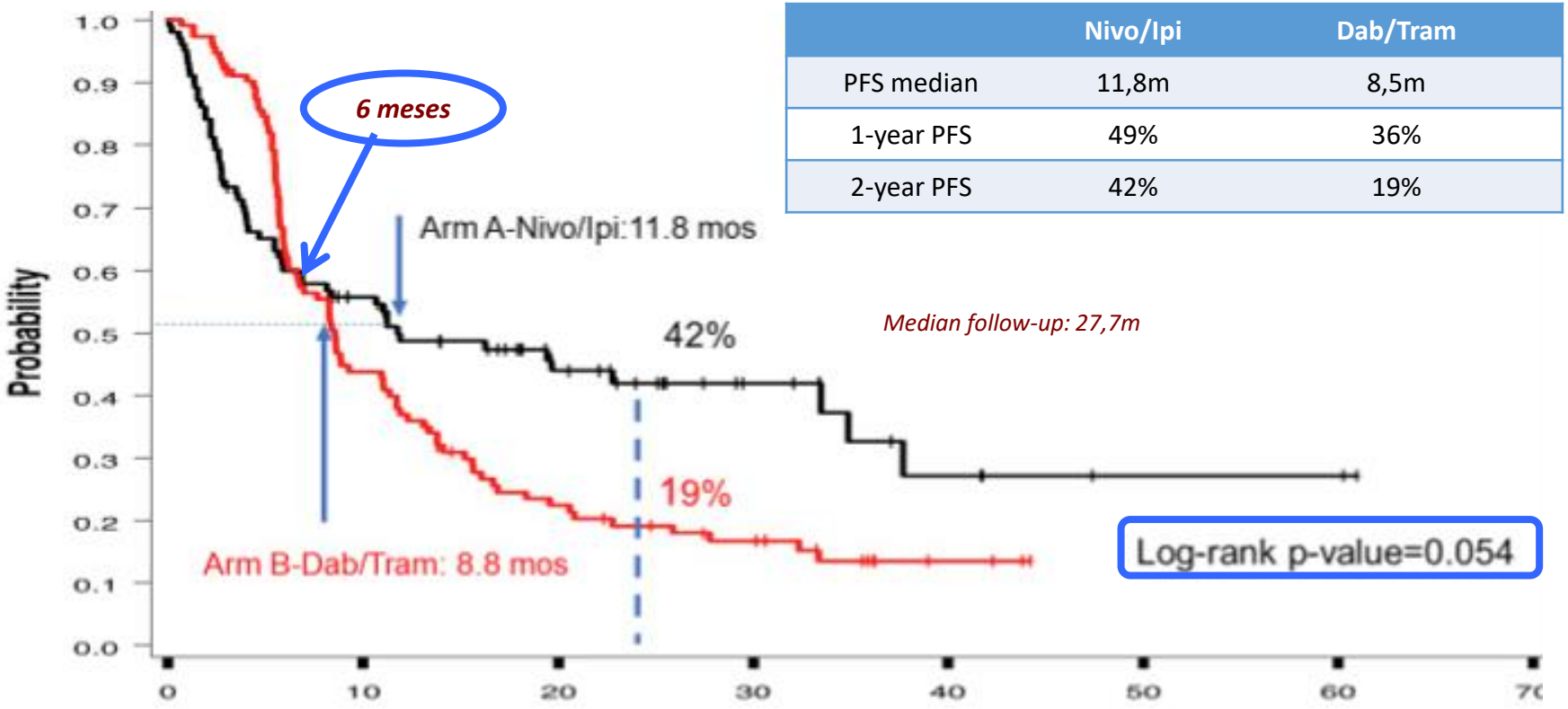
	Step 1		Step 2	
	Arm A-IO (n=126)	Arm B-TT (n=130)	Arm C-TT (n=26)	Arm D-IO (n=42)
Grade 3+ TRAEs (95% CI)	60% (51%, 69%)	52% (43%, 61%)	54% (33%, 73%)	50% (34%, 66%)
Grade 5 AEs (CTEP)^	11	10	3	3
Grade 5 TRAE	2*	0	1#	0

ASCO Plenary Series

Atkins M. J Clin Oncol 39, 2021 (suppl 36; abstr 356154)

DREAMseq: *Nivo/Ipi vs Dabra/Trame in 1st line*

Progression Free Survival (PFS): Step1 (n=214)



	Nivo/Ipi	Dab/Tram
PFS median	11,8m	8,5m
1-year PFS	49%	36%
2-year PFS	42%	19%

Median follow-up: 27,7m

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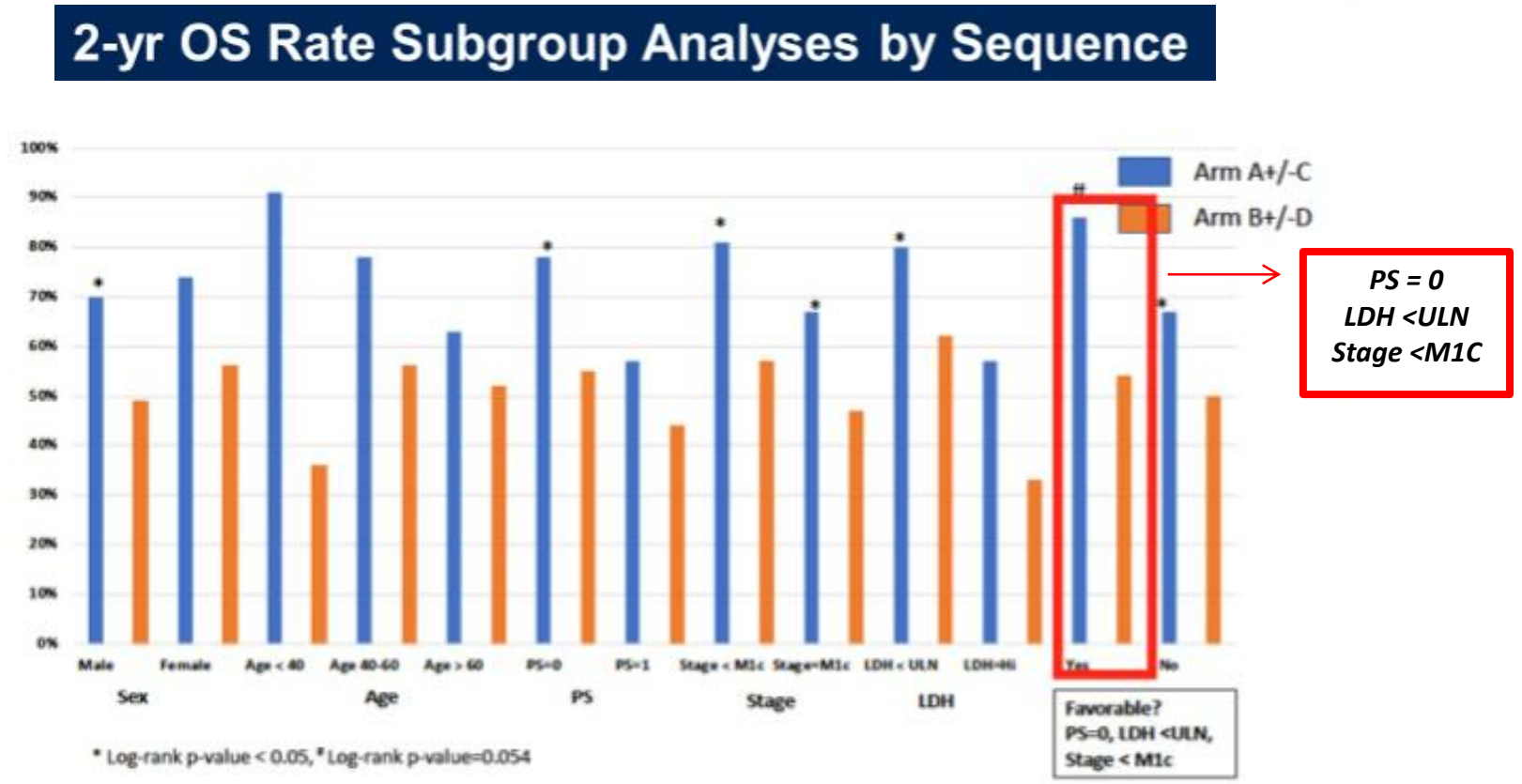
Atkins M. J Clin Oncol 39, 2021 (suppl 36; abstr 356154)

DREAMseq: *Nivo/Ipi vs Dabra/Trame in 1st line*



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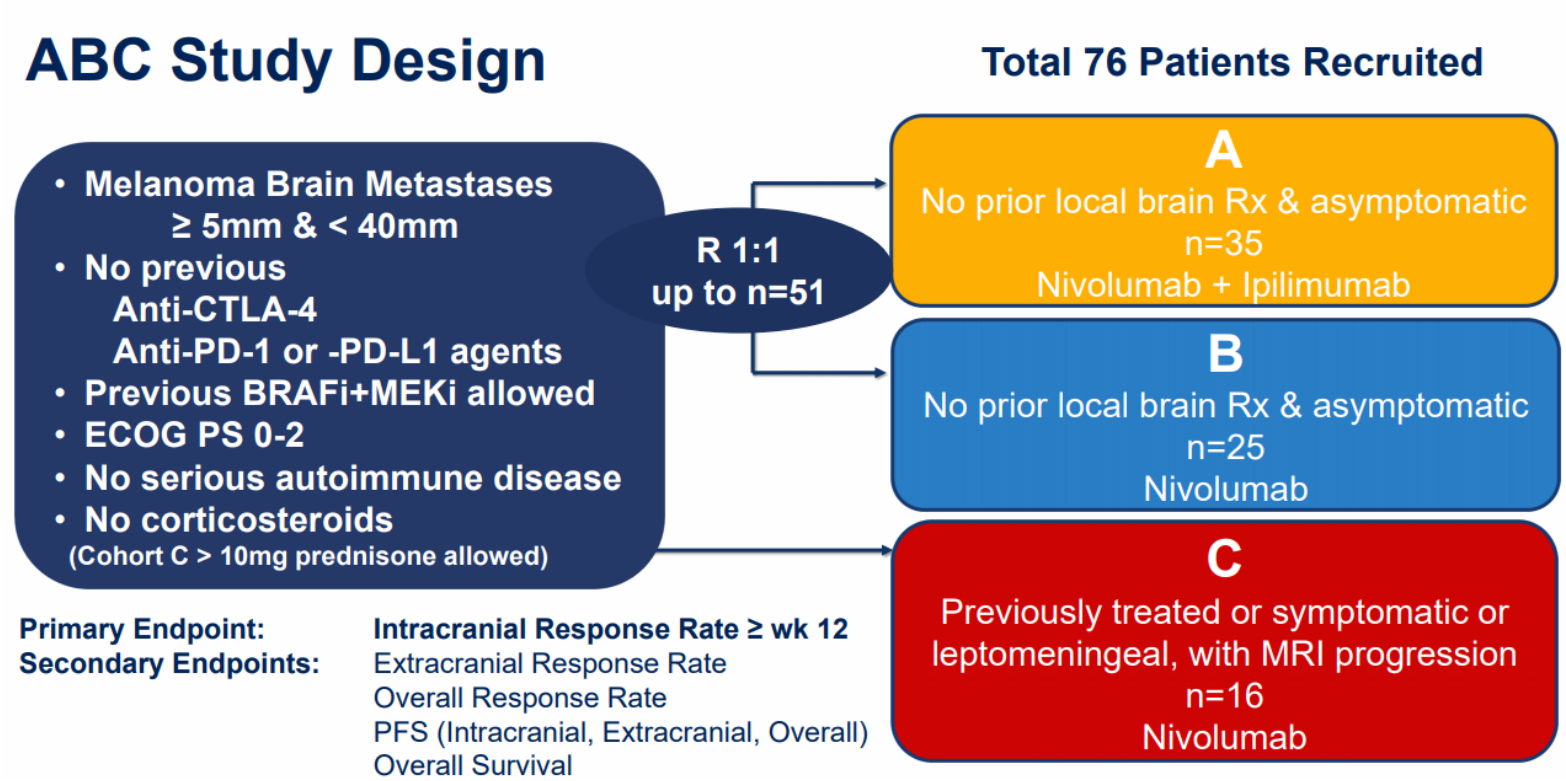
Atkins M. J Clin Oncol 39, 2021 (suppl 36; abstr 356154)

Five-year Overall Survival from the Anti-PD1 Brain Collaboration (ABC Study): Randomized Phase 2 Study of Nivolumab or Nivolumab + Ipilimumab In Patients With Melanoma Brain Metastases



GV Long et al Presented at the ASCO 2021

Five-year Overall Survival from the Anti-PD1 Brain Collaboration (ABC Study): Randomized Phase 2 Study of Nivolumab or Nivolumab + Ipilimumab In Patients With Melanoma Brain Metastases

ABC Best Intracranial RECIST Response

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**18 (51%)**	**5 (20%)**	**1 (6%)**
CR	9 (26%)	4 (16%)	0 (0%)
PR	9 (26%)	1 (4%)	1 (6%)
SD	2 (6%)	0 (0%)	2 (13%)
PD	14 (40%)	19 (76%)	13 (81%)
NE*	1 (3%)	1 (4%)	0 (0%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*Pts who deceased prior to wk 12 = PD
†Leptomeningeal, previous local treatment or symptoms

ABC Best Intracranial RECIST Response: *Drug Treatment Naïve Patients*

	A: Nivo+Ipi N=27	B: Nivo N=19
Intracranial Response, n (%)	16 (59%)	4 (21%)
CR	8 (30%)	3 (16%)
PR	8 (30%)	1 (5%)
SD	2 (7%)	0 (0%)
PD	8 (30%)	14 (74%)
NE*	1 (4%)	1 (5%)

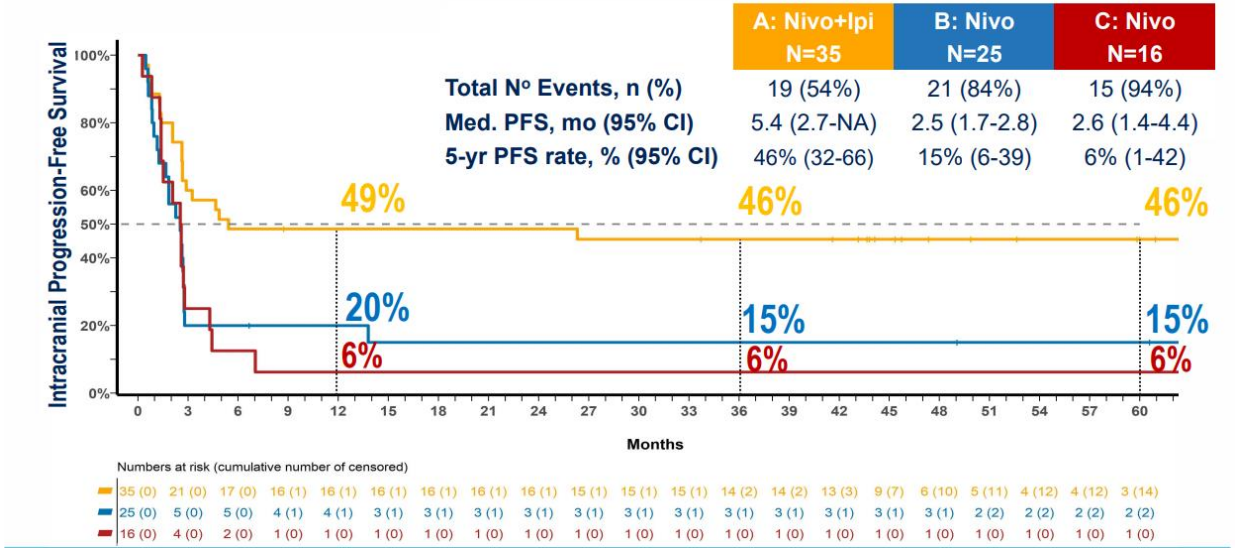
- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*Pts who deceased prior to wk 12 = PD

GV Long et al. ASCO 2021

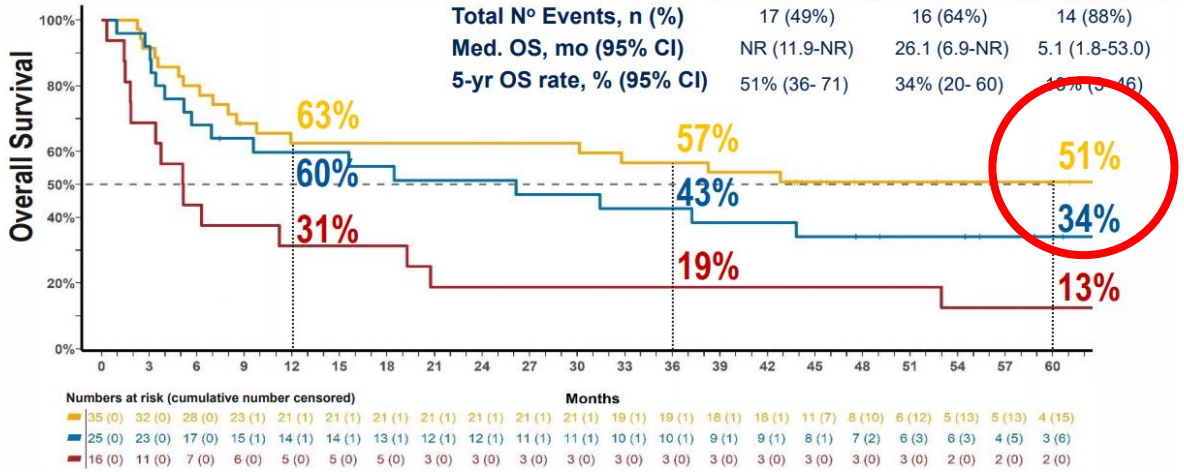
Five-year Overall Survival from the Anti-PD1 Brain Collaboration (ABC Study): Randomized Phase 2 Study of Nivolumab or Nivolumab + Ipilimumab In Patients With Melanoma Brain Metastases

ABC Intracranial Progression-Free Survival



	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	19 (54%)	21 (84%)	15 (94%)
Med. PFS, mo (95% CI)	5.4 (2.7-NA)	2.5 (1.7-2.8)	2.6 (1.4-4.4)
5-yr PFS rate, % (95% CI)	46% (32-66)	15% (6-39)	6% (1-42)

Overall Survival



	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	17 (49%)	16 (64%)	14 (88%)
Med. OS, mo (95% CI)	NR (11.9-NR)	26.1 (6.9-NR)	5.1 (1.8-53.0)
5-yr OS rate, % (95% CI)	51% (36- 71)	34% (20- 60)	[illegible]

- Death solely due to intracranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

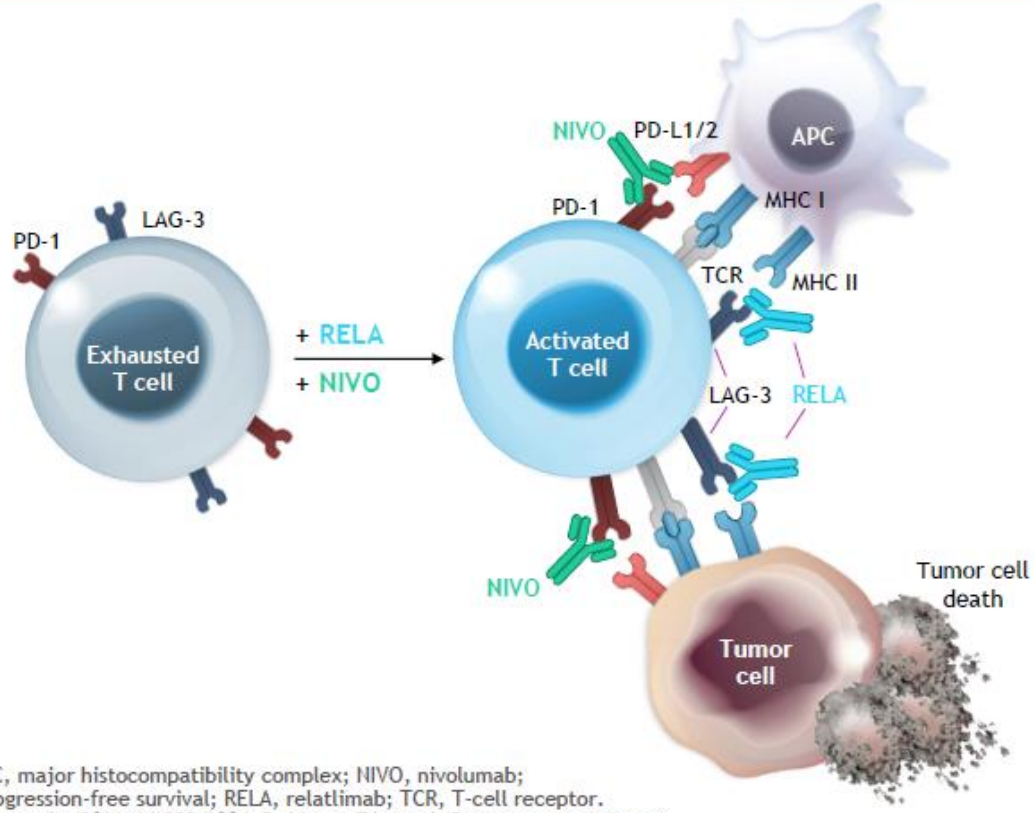
GV Long et al. ASCO 2021

ESQUEMA

1. INTRODUCCIÓN
2. INHIBIDORES DEL PUNTO DE CONTROL
3. “SITUACIONES ESPECIALES”
4. **ALGUNAS COMBINACIONES**
5. CONCLUSIONES

Introduction

- LAG-3 and PD-1 are distinct immune checkpoints, often co-expressed on tumor-infiltrating lymphocytes, and contribute to tumor-mediated T-cell exhaustion[1,2]
- RELA is a human LAG-3-blocking antibody that restores effector function of exhausted T cells[3]
- In RELATIVITY-047, RELA + NIVO demonstrated a significant PFS benefit, with a manageable safety profile, in previously untreated metastatic or unresectable melanoma[4]



APC, antigen-presenting cell; LAG-3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; NIVO, nivolumab; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PFS, progression-free survival; RELA, relatlimab; TCR, T-cell receptor.

1. Woo S-R, et al. *Cancer Res* 2012;72:917-927; 2. Anderson AC, et al. *Immunity* 2016;44:989-1004; 3. Lipson EJ, et al. Poster presentation at SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract P232; 4. Lipson EJ, et al. American Society of Clinical Oncology Congress; June 4-8, 2021. Abstract number 9503.

EJ Lipson et al Presented at ASCO 2021

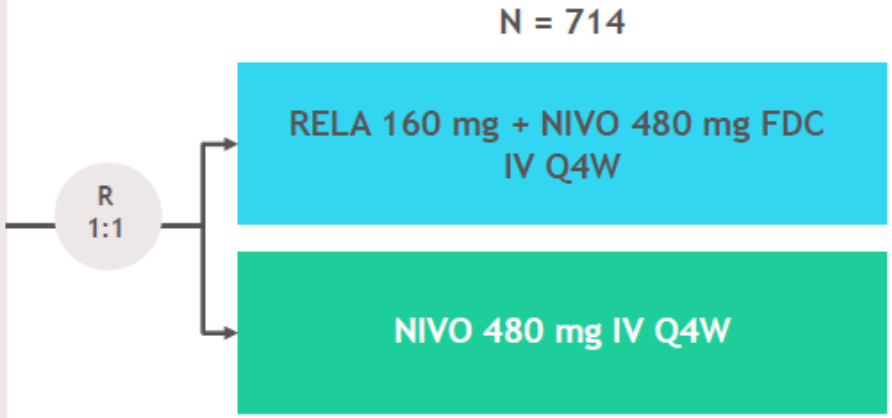
RELATIVITY-047

Study design

- RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated metastatic or unresectable melanoma[a]
- ECOG PS 0-1

Stratification factors
- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



Primary endpoint
- PFS by BICR[d]

Secondary endpoints
- OS
- ORR by BICR[d]

Exploratory endpoints included:
- TFI
- PFS2

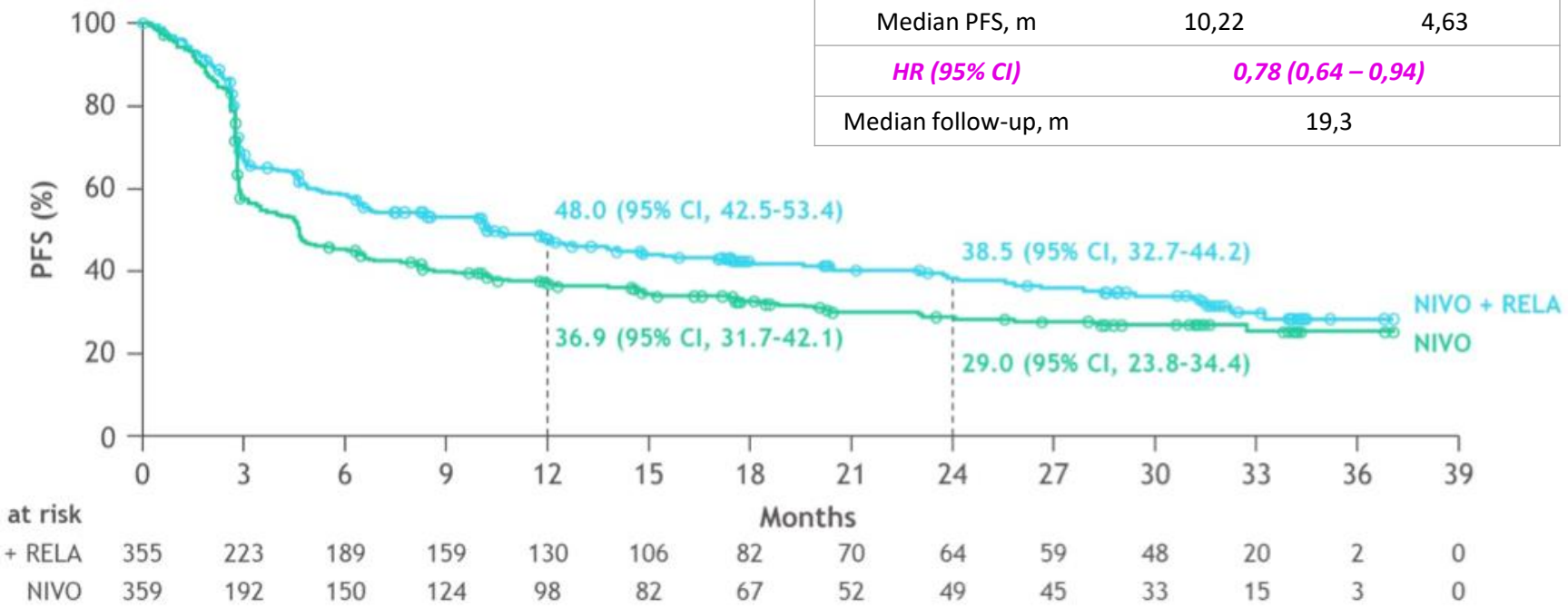
AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; FDC, fixed-dose combination; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS2, progression-free survival 2; Q4W, every 4 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TFI, treatment-free interval.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if ≥ 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was ≥ 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.
ClinicalTrials.gov: NCT03470922; Lipson EJ, et al. American Society of Clinical Oncology Congress; June 4-8, 2021. Abstract number 9503.

EJ Lipson et al Presented at ASCO 2021

RELATIVITY-047: *Overall survival and response rates*

Primary endpoint: updated PFS by BICR

	NIVO + RELA	NIVO
Median PFS, m	10,22	4,63
HR (95% CI)	*0,78 (0,64 – 0,94)*	
Median follow-up, m	19,3	

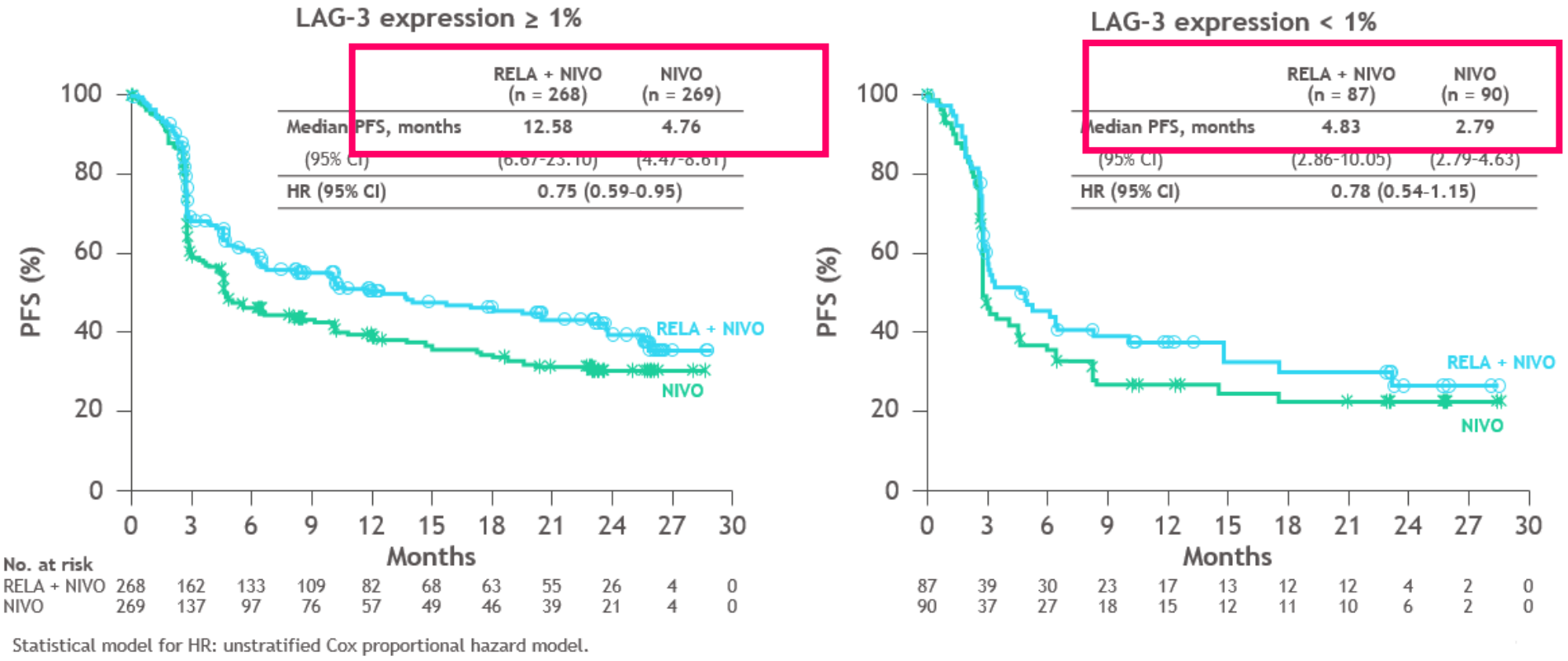


ASCO Plenary Series

Long GV et al. J Clin Oncol 40, 2022 (suppl 36; abstr 360385)

RELATIVITY-047

- PFS benefit favored RELA + NIVO FDC regardless of LAG-3 expression status



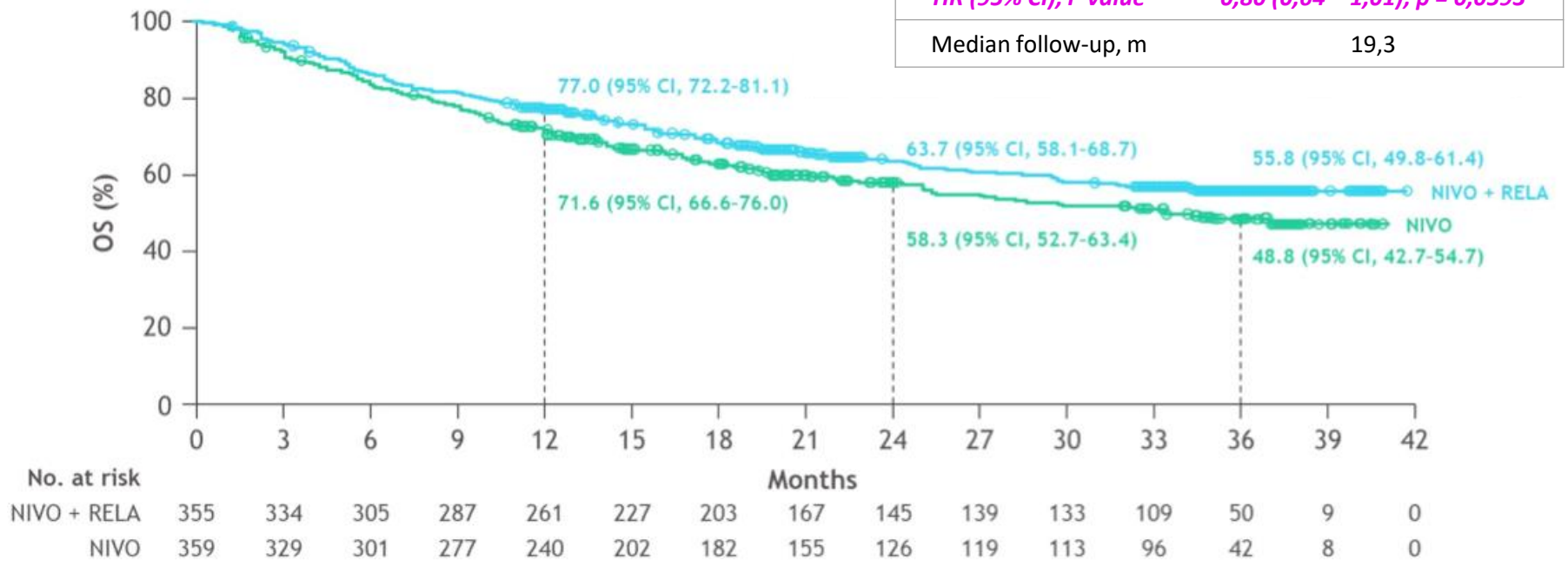
Statistical model for HR: unstratified Cox proportional hazard model.

EJ Lipson et al Presented at ASCO 2021

RELATIVITY-047: *Overall survival and response rates*

Secondary endpoint: overall survival

	NIVO + RELA	NIVO
Median OS, m	NR	34,10
HR (95% CI), P value	***0,80 (0,64 – 1,01); p = 0,0593***	
Median follow-up, m	19,3	



ASCO Plenary Series

Long GV et al. J Clin Oncol 40, 2022 (suppl 36; abstr 360385)

RELATIVITY-047: *Overall survival and response rates*

Secondary endpoint: confirmed ORR by BICR

Overall response	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR, n (%)	153 (**43.1**)	117 (**32.6**)
95% CI	37.9-48.4	27.8-37.7
Difference of ORR, % (95% CI)	10.3 (3.4-17.3)	
Odds ratio, % (95% CI)	1.6 (1.2-2.2)	
Confirmed best overall response, n (%)		
Complete response	58 (16.3)	51 (14.2)
Partial response	95 (26.8)	66 (18.4)
Stable disease	61 (17.2)	59 (16.4)
Progressive disease	105 (29.6)	149 (41.5)
Unknown	27 (7.6)	28 (7.8)
DCR, n (%)	223 (62.8)	182 (50.7)
95% CI	57.6-67.9	45.4-56.0
Median DOR, months	NR	NR
95% CI	29.57-NR	29.93-NR

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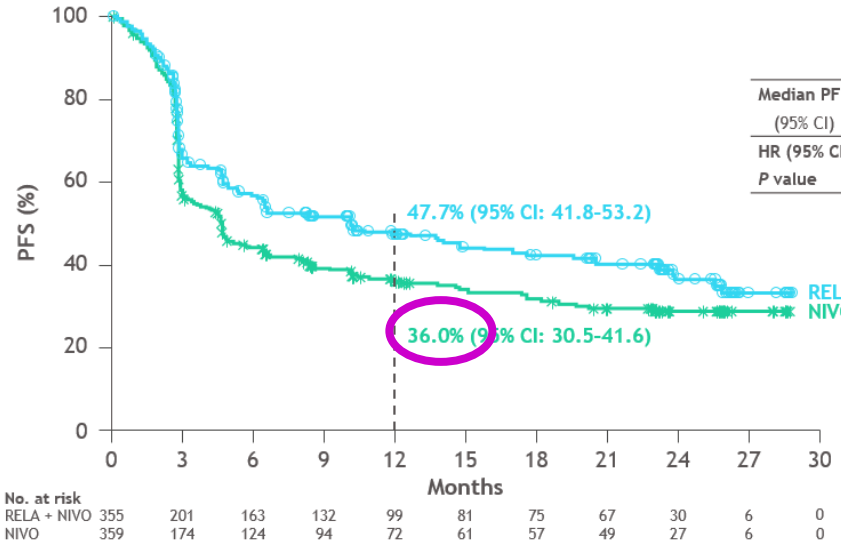
Long GV et al. J Clin Oncol 40, 2022 (suppl 36; abstr 360385)

Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
Leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths[a]	4 (1.1)	0	2 (0.6)	0

ASCO Plenary Series

Long GV et al. J Clin Oncol 40, 2022 (suppl 36; abstr 360385)



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

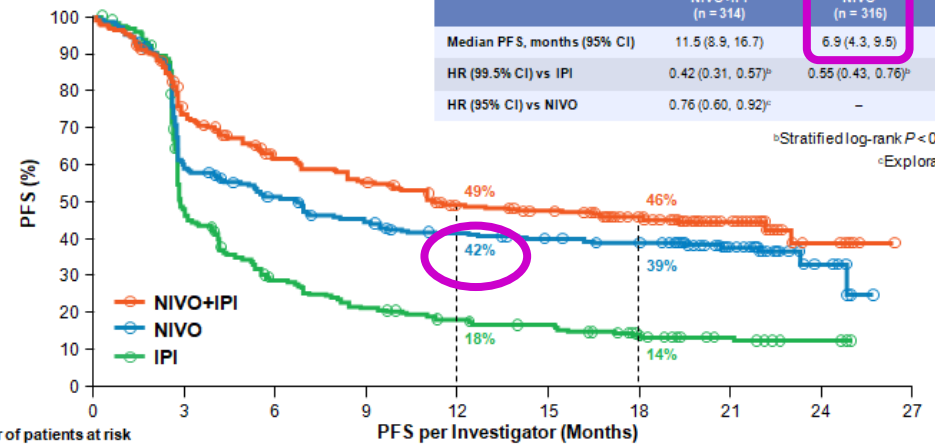
CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

BRAF mutado 38,3% en RELA vs 32% en CheckMate067
LDH elevada 36% en ambos grupos

PFS With the NIVO+IPI Regimen and NIVO Alone Versus IPI Alone[a] (CheckMate 067)

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
HR (99.5% CI) vs IPI	0.42 (0.31, 0.57)[b]	0.55 (0.43, 0.76)[b]	–
HR (95% CI) vs NIVO	0.76 (0.60, 0.92)[c]	–	–

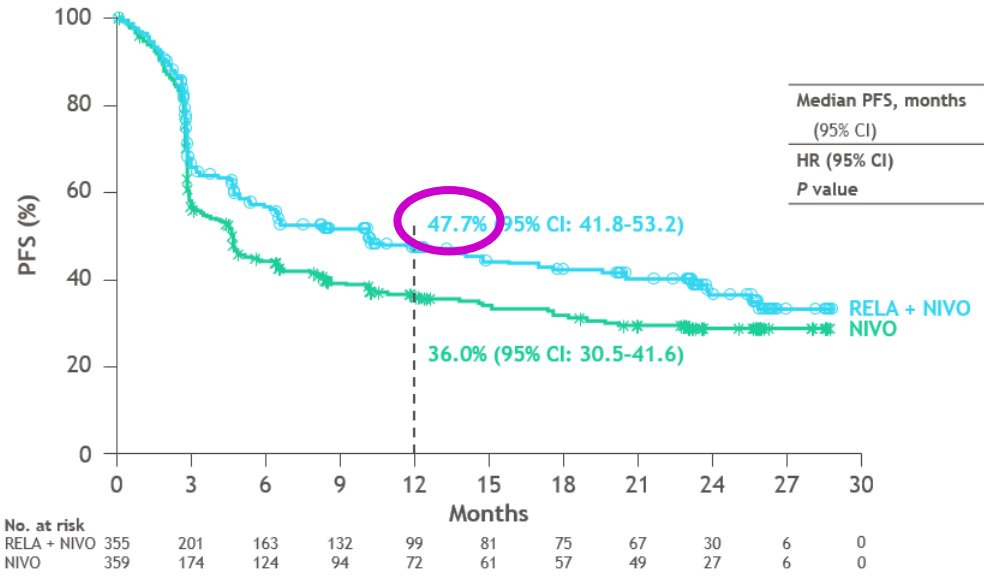
[b]Stratified log-rank $P < 0.00001$ vs IPI
[c]Exploratory endpoint



Number of patients at risk

NIVO+IPI	314	219	174	156	133	126	103	48	8	0
NIVO	316	177	148	127	114	104	94	46	8	0
IPI	315	137	78	58	46	40	25	15	3	0

[a]**Minimum of 18-month follow-up (ITT population).**
Database lock November 2015
ITT = intention-to-treat
Wolchok JD et al. Presented at ASCO 2016; abstract 9505



	RELA + NIVO (n = 355)	NIVO (n = 359)
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P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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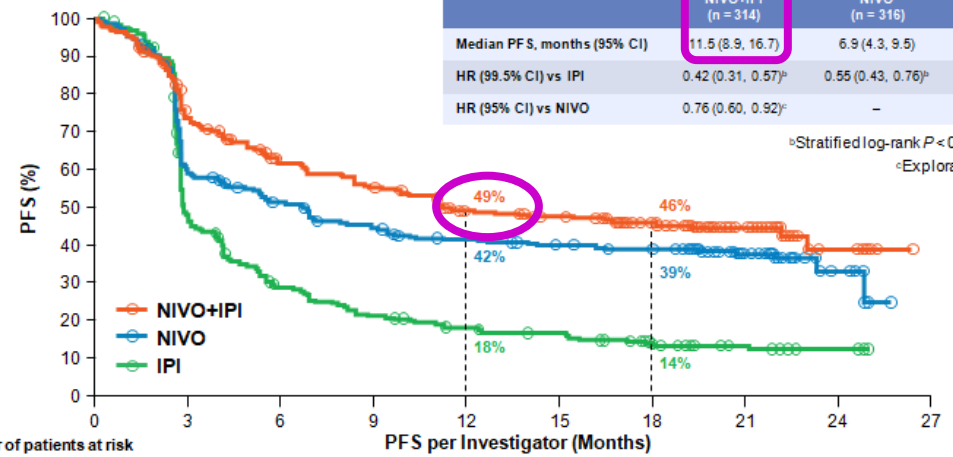


[a]**Minimum of 18-month follow-up (ITT population).**
Database lock November 2015
ITT = intention-to-treat
Wolchok JD et al. Presented at ASCO 2016; abstract 9505

Toxicity of relatlimab + nivolumab similar to that seen with nivolumab in CM067

AE, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
TRAE ≥ 10%				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)	
	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)

Larkin *et al*. *N Engl J Med*. 2015

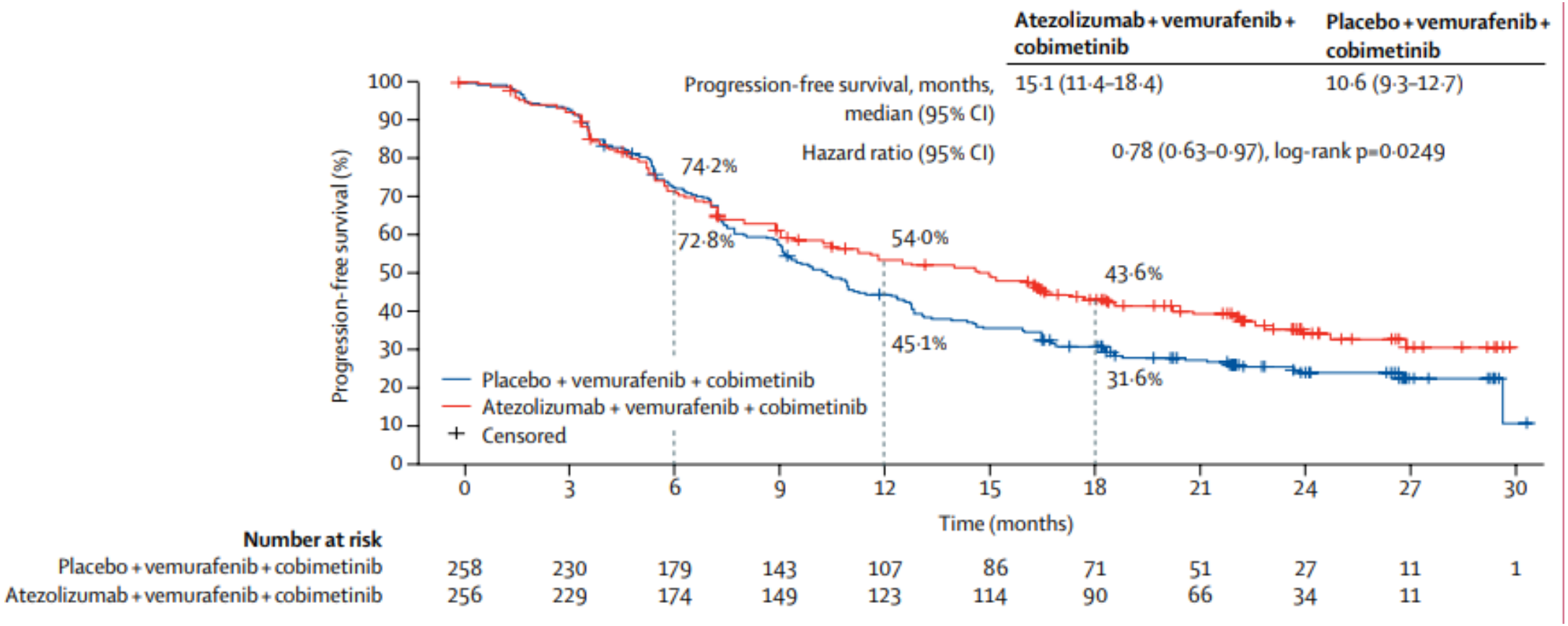
TRIPLETES EN BRAF MUTADOS

	KEYNOTE-022 *N* = 120		IMspire150 *N* = 514		COMBI-i *N* = 532	
	D + T + Pem	D + T + Pbo	V + C + Atezo	V + C + Pbo	D + T + Sparta	D + T + Pbo
Age, years	54	58	54	53.5	56	55
ECOG						
0	78	73	76	77	73	74
1	22	27	24	22	25	25
2	-	-	-	-	2	1
LDH at baseline > ULN (%)	45	43	33	33	39	40
Melanoma staging (%)						
IIIB	2	2	-	-	-	-
IIIC	0	3	5	6	6	6
IVa	3	17	16	14	11	16
IVb	13	15	22	16	21	14
IVc	82	63	57	63	62	65

Data for age is in median, all other data is %. *D + T*, dabrafenib and trametinib; *V + C*, vemurafenib and cobimetinib; *Pem.*, pembrolizumab; *Atezo.*, atezolizumab; *Sparta.*, spartalizumab; *Pbo*, placebo; *N*, number randomised; *ECOG*, Eastern Co-operative Oncology Group performance status; *LDH*, lactate dehydrogenase level; *ULN*, upper limit of normal. Melanoma staging is according to American Joint Committee on Cancer Melanoma Staging, 7th Edition

Julia R. Dixon-Douglas et al. Current Oncology Reports (2022) 24:1071–1079

Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAFV600 mutation positive* melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial



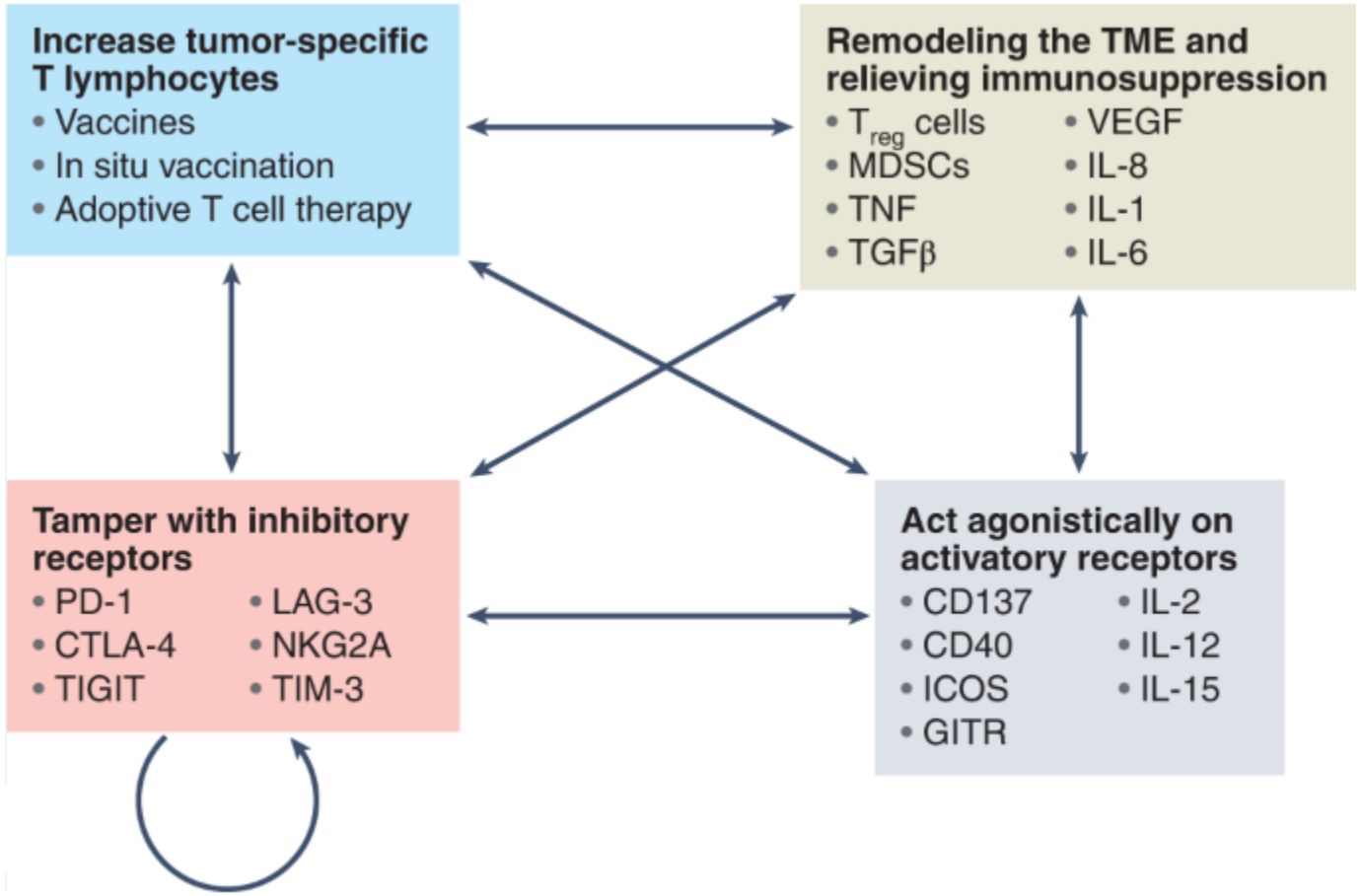
R. Gutzmer et al. ***Lancet 2020; 395: 1835–44***

IMspire150

	Atezolizumab + vemurafenib + cobimetinib (n=230)		Placebo + vemurafenib + cobimetinib (n=281)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any treatment-related adverse event	228 (99%)	182 (79%)	279 (99%)	205 (73%)
Treatment-related adverse events with a prevalence ≥10%*				
Blood creatine phosphokinase increased†	118 (51%)	46 (20%)	126 (45%)	42 (15%)
Rash	94 (41%)	20 (9%)	115 (41%)	25 (9%)
Diarrhoea	97 (42%)	4 (2%)	131 (47%)	9 (3%)
Arthralgia	90 (39%)	7 (3%)	79 (28%)	6 (2%)
Pyrexia	89 (39%)	3 (1%)	73 (26%)	3 (1%)
Alanine aminotransferase aspartate increased†	78 (34%)	30 (13%)	64 (23%)	25 (9%)
Lipase increased†	74 (32%)	47 (20%)	77 (27%)	58 (21%)
Aminotransferase increased†	69 (30%)	19 (8%)	57 (20%)	12 (4%)
Fatigue	62 (27%)	3 (1%)	74 (26%)	1 (<1%)
Nausea	54 (23%)	1 (<1%)	74 (26%)	7 (2%)
Pruritus	49 (21%)	2 (1%)	45 (16%)	1 (<1%)
Myalgia	48 (21%)	2 (1%)	35 (12%)	1 (<1%)
Photosensitivity reaction	48 (21%)	2 (1%)	70 (25%)	9 (3%)
Maculopapular rash	47 (20%)	29 (13%)	53 (19%)	27 (10%)
Amylase increased	46 (20%)	23 (10%)	45 (16%)	19 (7%)
Hyperthyroidism	39 (17%)	2 (1%)	21 (8%)	0
Hypothyroidism	38 (17%)	0	17 (6%)	0
Asthenia	37 (16%)	4 (2%)	39 (14%)	2 (1%)
Blood creatinine increased	36 (16%)	0	33 (12%)	1 (<1%)

R. Gutzmer et al. *Lancet 2020; 395: 1835–44*

NUEVAS COMBINACIONES



M.F. Sanmamed et al. Charting roadmaps towards novel and safe synergistic immunotherapy combinations. *Nat Cancer* 3, 665–680 (2022).

ESQUEMA

1. INTRODUCCIÓN
2. INHIBIDORES DEL PUNTO DE CONTROL
3. “SITUACIONES ESPECIALES”
4. ALGUNAS COMBINACIONES
5. **CONCLUSIONES**

CONCLUSIONES

- Los antiPD-1, solos o en combinación con anti-CTLA-4, han supuesto un nuevo paradigma en el tto del melanoma mtx, ya que son capaces de **aumentar la SG** y que esta **se mantenga a lo largo del tiempo**.
- El estudio **KEYNOTE-006** estaba diseñado para parar el tratamiento a los 2 años. Los pacientes en RC son los que más se benefician de esta posibilidad. A la recaída, el retratamiento con anti-PD-1 es una opción eficaz
- La combinación de **Nivolumab + Ipilimumab ha mostrado un 52% de pacientes vivos a 72 meses** pero con un **54% de toxicidades G 3-4**. El ILT con la combinación de ipi+nivo fue superior al de nivo
- Los antiPD-1 también pueden ser una opción de tratamiento en los pacientes **BRAF mutados**
- En los pacientes con **metástasis cerebrales asintomáticas la SG a 5 años** de los tratados con **Ipilimumab + Nivolumab fue del 51%**
- La combinación de **Rela + Nivo fue superior en SLP frente a Nivo (mediana 10,22 vs 4,63 meses),** aunque no disponemos de datos maduros de SG
- **La combinación de los inhibidores de puntos de control con otros inhibidores, vacunas o terapias oncolíticas pueden conseguir aumentar el número de largos supervivientes/pacientes curados**

MUCHAS GRACIAS